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CAUSE OF DEATH RESULTING FROM MASSIVE INFUSIONS OF ISOTONIC SOLUTIONS

AN EXPERIMENTAL STUDY

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The therapeutic status of intravenous infusion has undergone an important revision in the last few years. Just as the discovery of blood groups and their interrelations early in the present century made possible the extensive use of blood transfusions, so, more recently, has the discovery of the so-called "pyrogenic factor" in the causation of "infusion reactions" and of methods for its elimination made feasible the extensive use of intravenous infusions.

Prior to about ten years ago it was commonly held by well informed practicing physicians that intravenous injections were essentially dangerous because they always involved the risk of disrupting such compensatory mechanisms as those which maintain the acid-base balance, the osmotic tension and the viscosity of the blood. These mechanisms were conceived to be delicately balanced and easily upset. Accordingly, solutions for intravenous use were carefully compounded from "triple-distilled water" and if they were to be given in any considerable quantity were also carefully "buffered."

Physiologists had long known that experimental animals survive infusions of physiologic solution of sodium chloride, even though the solution is prepared without benefit of complicated physicochemical theories, in volumes far exceeding any ever used clinically;[1] but when using these solutions clinicians encountered "infusion reactions" in man which are not recognized, or at least are encountered only in very mild forms, in the lower animals. In spite of the fact that the outstanding clinical features of such reactions were chills and fever, almost every conceivable theory of their causation was entertained except the obvious

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1. Dastre, A., and Loye, P.: Le lavage du sang, Arch. de physiol. norm. et path. **2**:93-114, 1888.

one that something in certain solutions, not present in others, affected the temperature-regulating mechanism of the body. Man, possessing a more unstable temperature-regulating mechanism than other animals, would naturally be particularly susceptible to the effects of such an entity.

Not until the painstaking experimental investigations of Rademaker,[2] based on preceding observations by Seibert,[3] were published did the real source of the "infusion reaction" come to be appreciated. As a result of these investigations and others substantiating them [4] has come the installation of "solutions laboratories" in the larger hospitals. In these laboratories scrupulous care is exercised in the preparation of solutions and apparatus so that they are free from reaction-producing contaminations. Another result is the commercial production by medical supply houses of complete infusion outfits containing any of the solutions at present considered useful, together with the necessary rubber tubing and needles. These are prepared in convenient sterile packages, ready for immediate use and conforming with the highest laboratory standards.

Such developments in technic have reduced the incidence of infusion reactions so near to the vanishing point that hypodermoclysis and proctoclysis are rapidly becoming obsolete in many institutions. It has recently been felt by many physicians that this release from what amounted to a superstition, accomplished without introducing into the solutions themselves any substance except the chemically pure dextrose, sodium chloride or other simple chemical compounds and the distilled water in which they are dissolved, opens the way to new dangers which are likely to be engendered by undue confidence.[5] Because of the natural tendency to overdo any form of therapy which is relatively free from immediate danger, it seems that the time is now ripe for a more extensive laboratory appraisal than has yet been made of the basic responses to massive infusions. To assume that such simple solutions of dextrose and sodium chloride as are commonly used as vehicles are assimilated and utilized in precisely the same manner as they would be if they were absorbed from the intestinal tract and that

2. Rademaker, L.: The Cause and Elimination of Reactions After Intravenous Infusions, Ann. Surg. **92**:195-201, 1930; Reactions After Intravenous Infusions: A Further Study on Their Elimination, Surg., Gynec. & Obst. **56**:956-958, 1933.

3. Seibert, F. B.: Fever-Producing Substances Found in Some Distilled Waters, Am. J. Physiol. **67**:90-104, 1923.

4. Co Tui; McCloskey, K. L.; Schrift, M., and Yates, A. L.: A New Method of Preparing Infusion Fluids Based on the Removal of Pyrogen by Filtration, J. A. M. A. **109**:250-252 (July 24) 1937.

5. (*a*) de Takáts, G.: Push Fluids: Surgeons' Postoperative Order, Am. J. Surg. **11**:39-44, 1931. (*b*) Fantus, B.: Fluid Postoperatively: A Statistical Study, J. A. M. A. **107**:14-17 (July 4) 1936.

the reactions of the circulation to the effects of bulk or volume can be predicted or explained on the basis of what is already known of hemodynamics, until checked by laboratory data, is distinctly gratuitous.

In our laboratory we have been performing certain simple but fundamental experiments designed to test the intermediate and ultimate fate of the simpler solutions, particularly of sodium chloride and dextrose, which are so commonly used clinically in considerable volumes for intravenous infusion.

In a previous report [6] we described some of the physiologic responses of the cat to massive infusions of 1 per cent sodium chloride solution. In the present communication we have to report some observations on the infusion of 5 per cent dextrose solution. These observations, in conjunction with previously reported and as yet unreported additional data on sodium chloride solution, seem to present a virtually complete picture of the cause of death when isotonic solutions of these two substances are injected at excessive rates and in excessive amounts.

METHOD

As in the previous series of studies, cats were used as experimental animals. The solutions were injected by gravity from an arsphenamine buret, which was ordinarily raised to such a level that the height of the column of fluid above the cannula varied from about 25 inches (63 cm.) when the tube was full to about 16 inches (40.5 cm.) when the level of the fluid had dropped to the last graduation. Additionally, however, we have on a number of occasions used a gravity system in which the height of the fluid reservoir above the animal was about 6 feet (182.8 cm.) and with which the rate of flow was adjusted to a constant volume output by a screw clamp and a glass dropping tube without any vent; this was in an attempt to stabilize the rate of delivery of fluid against minute variations by increasing the head of pressure. This modification of technic was found to offer no particular advantages over the original method, but as a check it is perhaps of some importance. Solutions were injected at approximately body temperature in all instances. Some experiments have been performed in which the temperature was accurately controlled by an electric heating device and thermometer placed just proximal to the cannula inserted into the vein of the animal. This refinement of technic, however, was found to be of little importance except as a check on the ordinary procedure of preheating the solution to a temperature sufficiently higher than that of the body to allow for the unavoidable loss of heat as the solution flows through the delivery system.

RATE AND VOLUME RELATIONS OF LETHAL DOSES OF ESSENTIALLY ISOTONIC SOLUTIONS OF SODIUM CHLORIDE AND DEXTROSE

In tables 1 and 2 are recorded representative data from experiments designed to determine the maximal rates at which prolonged infusions

6. Cutting, R. A.; Lands, A. M., and Larson, P. S.: Distribution and Excretion of Water and Chlorides After Massive Saline Infusions: An Experimental Study, Arch. Surg. **36**:586-613 (April) 1938.

can be given and the total amounts which can be infused before death supervenes. Only observations obtained under the most carefully controlled conditions have been included in the tables. Although the number of cases shown in table 1 is less than the number shown in table 2, the average value is probably as reliable in the one instance as in the

TABLE 1.—*Lethal Doses of 1 Per Cent Sodium Chloride Solution*

Animal Number	Weight in Kilograms	Rate of Infusion, Cc./Kg./Min.	Total Amount Infused, Cc./Kg.	Retained Fluid, Cc./Kg.	
				Including Peritoneal Fluid	Not Including Peritoneal Fluid
S-35	2.10	3.7	679	575	468
S-36	1.70	5.6	727	495	423
S-37	1.90	5.8	606	522	450
S-38	1.70	4.8	742	519	446
S-39	1.75	5.7	777	666	540
Mean		5.1	706.2	555.5	465.4
Mean variation			7.2 per cent	9.4 per cent	6.7 per cent

TABLE 2.—*Lethal Doses of 5 Per Cent Dextrose Solution*

Animal Number	Weight in Kilograms	Rate of Infusion, Cc./Kg./Min.	Total Amount Infused, Cc./Kg.	Retained Fluid, Cc./Kg.	
				Including Peritoneal Fluid	Not Including Peritoneal Fluid
S-13	2.57	3.8	535	352	294
S-14	2.15	4.1	405	358	299
S-16	2.35	3.5	511	345	286
S-17	2.15	3.9	368	300	280
S-18	2.30	3.3	391	370	319
S-19	2.60	4.0	433	291	255
S-22	2.45	4.2	531	409	384
S-25	2.80	4.5	516	339	296
S-26	2.10	4.8	350	309	283
S-27	2.40	4.6	406	358	322
S-31	1.95	4.8	559	328	274
S-32	2.05	4.5	450	387	328
S-33	2.00	4.8	393	320	279
S-40	2.60	4.6	574	344	311
S-41	2.37	4.0	557	376	339
Mean		4.2	465.3	345.7	303.2
Mean variation			15.1 per cent	7.33 per cent	8.05 per cent

other, for in both instances the averages have been checked against considerably larger series of not quite so well controlled experiments.

In explanation of the recorded values, it should be emphasized that the rates called "maximal" refer to prolonged injections, not to speeds of injection which are initially tolerated or which can be maintained at odd intervals for short periods. It should be obvious that compensatory mechanisms which may be adequate during the first minutes of a massive infusion may fail as the cumulative strain of infusion during many

minutes becomes felt, or that repeated surges of strain of short duration may fail to break down compensatory mechanisms which would succumb under continuous pressure of similar magnitude.

As will immediately be seen, it is possible to give 1 per cent saline solution considerably more rapidly and in considerably larger total amounts than 5 per cent dextrose solution. With cats, it is possible to infuse 1 per cent saline solution at rates averaging 5.1 cc. per kilogram of body weight per minute, whereas for 5 per cent dextrose solution the maximal rate of infusion averages only 4.2 cc. per kilogram per minute. Cats tolerate saline solution in total amounts up to 706 cc., whereas they tolerate dextrose solution in total amounts up to only 465 cc. per kilogram of body weight.

All the infusions represented in these two tables were carried to the actual death of the animals. The volumes of retained fluid, tabulated in the last two columns, were calculated by subtracting from the total volume of fluid infused the volume of urine which, during the infusion, drained away through a retention catheter introduced into the bladder. The mathematical difference between the figures in the last two columns for each animal represents the amount of peritoneal fluid collected from the abdominal cavity directly after death. As might reasonably be expected, the amount of retained fluid for animals given lethal doses of saline solution was considerably greater than that for animals to which the dextrose solution had been administered (in the ratio of 555 to 345 cc. per kilogram of body weight, including peritoneal fluid).

With only such values before one, it might seem logical to conclude that because the rate and volume tolerated in the case of saline solutions are so definitely greater than the rate and volume in the case of dextrose solutions, the chemical composition of the infused fluid must be the important factor in causing death. As a matter of fact, a study of the changes in blood pressure associated with massive infusions seems to indicate otherwise, at least as far as the immediate cause of death is concerned.

BLOOD PRESSURE CHANGES RESULTING FROM MASSIVE INFUSIONS

Chart 1 is a kymographic record of respiratory and arterial blood pressure responses to a lethal infusion of 5 per cent dextrose solution. In every essential respect, the tracing, which is representative for dextrose solutions, conforms to tracings obtained during infusions of 1 per cent saline solutions.[6] The respiratory portion of the kymogram shows nothing of particular importance except for a period of hyperpnea associated with vomiting, which the animal showed relatively early in the infusion, and a gradual progressive increase in the amplitude of respirations as more and more of the solution accumulated in the body

of the animal, especially (toward the end of the infusion) in the abdominal cavity; as the animal became overwhelmed, the amplitude of the respirations again diminished to the point of final apnea.

The tracing of the arterial pressure shows in the first fifteen minutes a slight increase in mean systolic pressure; this, however, did not exceed 10 mm. of mercury. With the attack of vomiting the pressure decreased in typical fashion. As the animal became overwhelmed by the infusion the pulse pressure increased progressively, whereas the mean arterial blood pressure decreased to the terminal stages of failure of the

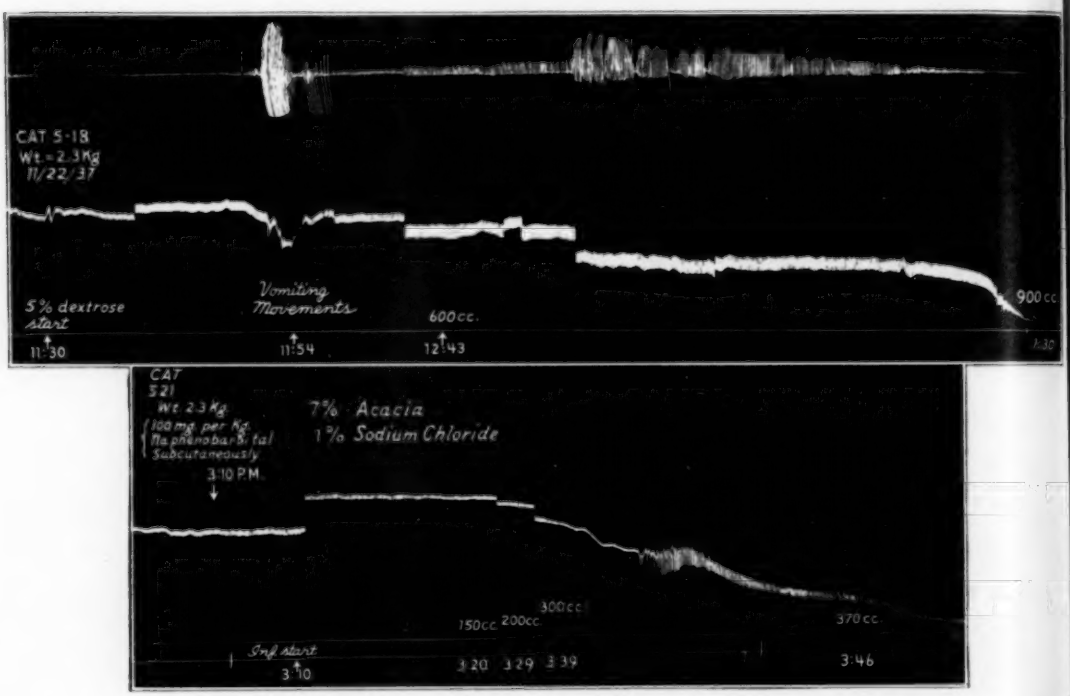

Chart 1.—The upper portion of the chart represents the response of the blood pressure of the cat to a lethal infusion of 5 per cent dextrose solution. The lower portion represents the response of the blood pressure to a lethal infusion of "gum-saline" solution (7 per cent acacia in 1 per cent solution of sodium chloride).

circulation. Though the condition is not well shown in this particular tracing, the last few minutes of infusion was characteristically associated with bradycardia.

The kymogram at the bottom of the figure represents a typical response of the arterial blood pressure to a lethal infusion of 7 per cent acacia in 1 per cent sodium chloride solution, the familiar "gum-saline" solution used clinically. Both the upper tracing and the lower one have been considerably telescoped for purposes of reproduction, but not in

exactly the same proportion; the lower tracing, in order to be strictly comparable, should have been shortened to only a little more than one-third the length of the upper one. It takes approximately two and one-half times as much 5 per cent dextrose solution as gum-saline solution to cause death when the two are given at comparable rates, and, accordingly, an animal given 5 per cent dextrose solution survived almost three times as long as one given gum-saline solution. Except for this, however, the changes in the arterial blood pressure are similar; the early increase in mean arterial pressure is in evidence, amounting in this instance to about 36 mm. of mercury, and as the animal becomes overwhelmed by the solution the progressive decrease in mean arterial pressure, the increase in pulse pressure and the terminal bradycardia are all well shown.

The suggestion is obvious that all three solutions, physiologic sodium chloride, physiologic dextrose and physiologic acacia, when infused in massive amounts cause death by overloading the circulation. Further evidence of this is afforded by a study of responses of the circulating blood volume and by estimations of venous pressure.

EFFECT OF MASSIVE INFUSIONS ON CIRCULATING BLOOD VOLUME AND VENOUS PRESSURE

It seems highly improbable that any method now in use for the estimation of true blood volume, plasma volume or red cell volume is capable of close or accurate interpretation. This is, without doubt, particularly true under conditions which tend to change blood volume profoundly, such as severe hemorrhage or massive infusion. The reason seems to lie in the impossibility of differentiating between vascular changes due to gain or loss of fluid and those due to vasomotor or circulatory changes.[7] No special comment need be made on the well recognized fact that under changing conditions the total bulk of the blood within the entire vascular tree is capable of relatively rapid gains or losses by virtue of the passage of water and certain other substances in solution from the terminal ramification of the vessels to the extravascular tissue spaces and vice versa. The effect of vasomotor or circulatory changes is not quite so obvious. There is some evidence that at least two important mechanisms may be operative. One of these leads to the stagnation of concentrated blood in certain areas of the body. Krogh, cited by Hooper and his associates,[8] illustrated this par-

7. Lampson, P. D., and Rosenthal, S. M.: Inadequacy of Our Present Blood Volume Methods, Am. J. Physiol. **63**:358-367, 1923.

8. Hooper, C. W.; Smith, H. P.; Belt, A. E., and Whipple, G. H.: Blood Volume Studies: Experimental Control of a Dye Blood Volume Method, Am. J. Physiol. **51**:205-220, 1920.

ticular mechanism in his description of the physiologic effect of applying a small drop of ethyl carbamate (urethane) solution to a single narrow capillary and arteriole in the mucous membrane of the frog's tongue:

> While the arteriole remains narrow, the capillary dilates more and more as the blood flows into it and little or no blood flows out from the venous end, but at the same time, the concentration of the blood is visibly increased from moment to moment. The corpuscles become packed together, forming a solid clump near the venous end; this clump grows into a long column by fresh corpuscles being added to it. One is able to watch quite distinctly how the plasma disappears from the normal blood entering the capillary, while the corpuscles are piled up until, finally, the whole strongly dilated capillary is completely filled and we have the typical stasis. The entire plasma, with all its colloids, is filtered off through the capillary wall. . . . A number of other observations and experiments show that the increased permeability cannot be due to any specific action of the ethyl carbamate but is a regular accompaniment of dilatation quite irrespective of the manner in which the dilatation is brought about.[9]

The other mechanism seems to provide for local dilution of the blood in certain areas and thus is the antithesis of the mechanism just described. Illustrative of the evidence for its existence is the following: Miller and Poindexter[10] found no demonstrable increase in circulating blood volume, as measured by the dye method, following rapid intravenous administration of rather large quantities of 0.9 per cent sodium chloride solution; hematocrit readings, on the other hand, indicated an average dilution of about 20 per cent. Crandall and Roberts[11] found the same discrepancy between the two methods of determining circulating volume following injections of 5 per cent dextrose solutions. They attempted to explain this on the basis of the hypothesis that the added fluid dilutes the blood in certain vessels, particularly those in the splanchnic area, to a greater extent than is the case elsewhere in the body, for they found that if they infused 50 to 100 cc. per kilogram of body weight of isotonic dextrose or saline solution into dogs with Eck fistulas, estimations of the blood volume by the dye method showed a definite increase in 4 out of 5 animals, accounting for as much as 40 to 50 per cent of the injected fluid.

Meek and Eyster[12] have shown, by means of photomicrographs of the capillaries and venules of the ear of the dog after intravenous

9. Krogh, A.: The Anatomy and Physiology of Capillaries, New Haven, Yale University Press, 1923.

10. Miller, J. R., and Poindexter, C. A.: The Effects Observed Following the Intravenous and Subcutaneous Administration of Fluid: An Experimental Study on Dogs, J. Lab. & Clin. Med. **18**:287-297, 1932.

11. Crandall, L. A., Jr., and Roberts, G. M.: Blood Volume After Intravenous Fluid in Normal and Eck Fistula Dogs, Am. J. Physiol. **101**:24-25, 1932.

12. Meek, W. J., and Eyster, J. A. E.: Reactions to Hemorrhage, Am. J. Physiol. **56**:1-15, 1921.

injection of acacia-saline solution, that these vessels act as reservoirs preventing any increase in the volume of the effective circulation. Thaysen [13] stated that if the erythrocytes were counted systematically over long periods in cases of polycythemia, remarkable fluctuations in the count would probably be found. He reported a case in which the erythrocyte count ran in the course of twelve hours from 5,300,000 to 10,600,000. His investigations and tests showed that the fluctuations were caused by varying contraction and dilatation of the capillaries and precapillaries of the skin.

Hooker [14] summarized the situation as follows:

> If the body has at its control such a highly organized device for the disposition and partition of the blood by which extensive capillary beds may be largely emptied of or packed with corpuscular elements or plasma, an explanation is readily found for the uncertainties of blood cell counts and blood volume determinations. Individual capillaries may be opened up or closed or they may be gorged with stagnant inactive corpuscles, as is possible to demonstrate on the finger. Mediation of these and similar changes would be accomplished by activation of the arteriole, capillary or venule functioning individually or collectively. It is natural to infer that normally such forces are well balanced and counteract one another so that the volume and corpuscular composition of the blood is held relatively stable, but in time of physiological stress or in disease the alterations which develop might assume considerable proportions.

Our experiments confirm the observation of others that although repeated estimations of the hemoglobin content during the course of a massive infusion seem to indicate that the circulating blood is undergoing considerable dilution, estimations of the blood volume according to "dye methods" give evidence that the increase in volume may be only moderate. Thus, in a typical experiment, assuming the normal circulating blood volume of the cat to be 63 cc. per kilogram of body weight (actual average for 11 animals), we found that after infusion of 200 cc. of 1 per cent saline solution per kilogram of body weight, the circulating volume as determined by the dye method was 78.7 cc. per kilogram, whereas hemoglobin dilution indicated a circulating volume of 104 cc. per kilogram.

With the reservations implied in the foregoing discussion of the value of hemoglobin dilution as a measure of circulating blood volume, the following data are presented:

Chart 2 shows simultaneous comparisons of "blood volume" estimated by the hemoglobin dilution method and estimations of venous pressure in animals given lethal infusions of 1 per cent saline solutions, and chart 3 shows similar comparisons for animals given lethal infusions of 5 per cent dextrose solutions.

13. Thaysen, T. E. H.: Polycythemia, abstracted, J. A. M. A. **75**:72 (July 3) 1920.

14. Hooker, D. R.: The Functional Activity of the Capillaries and Venules, Am. J. Physiol. **54**:30-53, 1920.

The upper portion of each figure is a graph in which a large number of estimations of blood dilution have been plotted on the basis of changes in hemoglobin concentration of the blood. The hemoglobin dilution is plotted vertically, and the volume of infused solution per kilogram of body weight of the animal is plotted horizontally; the horizontal ordinate can, of course, be used as an approximate measure of the duration of infusion, inasmuch as rates of infusion were comparable in all cases.

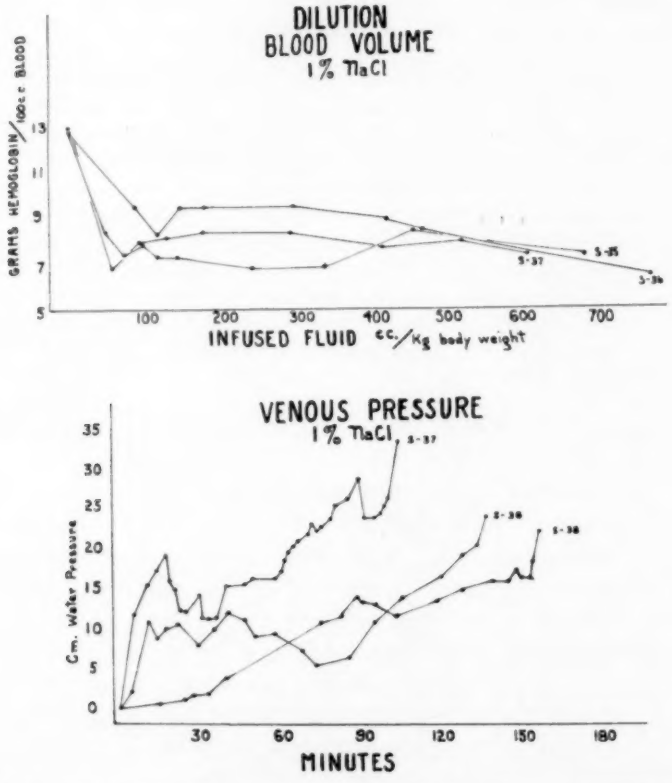

Chart 2.—The upper curve is a graph showing dilution of hemoglobin. For reasons explained in the text the hemoglobin dilution may not be taken as a direct measure of the magnitude of changes in the blood volume, but the conclusion seems unavoidable that some increase in circulating blood volume does occur as a large infusion progresses, as suggested by this curve, and explains at least in part the increase in venous pressure which is graphically shown in the lower curve. Such a view is certainly in accord with the observation of Meek and Eyster [16] that increase in stroke volume and increase in diastolic size of the heart results from intravenous infusions and our own observation (fig. 1) that increased pulse pressure without bradycardia (except terminally) occurs.

The lower graph in each of the two figures represents venous pressure in centimeters of water, as measured by a simple single-armed water manometer filled with physiologic solution of sodium chloride and connected by a short piece of rubber tubing to a cannula introduced into one of the external jugular veins of the animal. The error introduced by treating the pressure of the saline solution as pure water pressure is negligible.

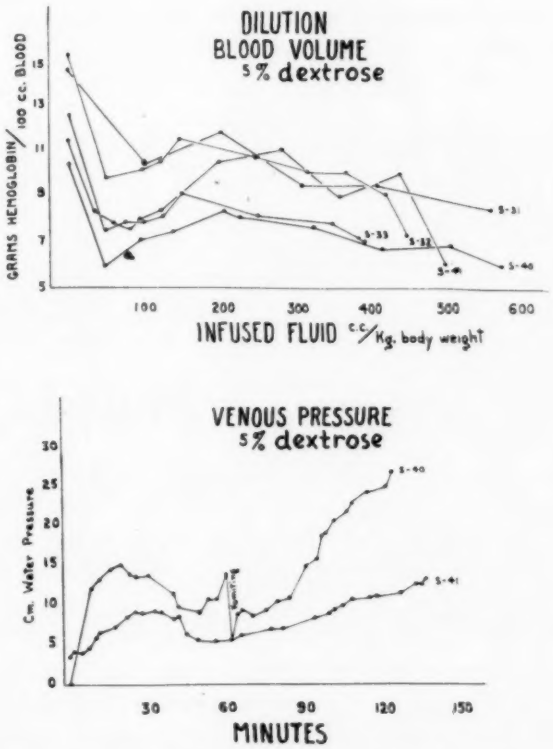

Chart 3.—The treatment and interpretation are the same as for figure 2. Dextrose instead of saline solution was used.

The most important feature of the venous pressure curves is the progressive increase as more and more fluid is infused. In most cases more than a third of the entire increase in venous pressure occurs within the first fifteen minutes of the infusion period; in other words, the curves commence with an abrupt rise.

The obvious explanation for this is that the added fluid increases the bulk of the circulating blood, and the venous blood pressure therefore rises.

Following the initial period characterized by an increase in the venous pressure there occurs a phase of reversal which we are rather at a loss to explain. During the ensuing period of approximately thirty minutes, i. e., in the interval from fifteen to forty-five minutes, the hemoglobin concentration increases slightly, while the venous pressure declines slightly. Inasmuch as during this period the infusion was continued at the same regular rate as before, the explanation must obviously be sought either in an unusually rapid diffusion of water out of the vascular system (such that diffusion actually occurred faster than fluid was added to the circulation) or in some relative addition to the circulation of hemoglobin in the form of red blood cells, such as might occur as a result of contraction of the spleen. Of the two possible explanations the former seems the more probable, especially in view of the fact that the phenomenon occupies a considerable period, during which additional water is being rapidly poured into the circulation. Although we have no evidence to indicate that such is the case, it is possible that during this period some special storage reservoir of the body, such as the peritoneal cavity, is rapidly opened. Perhaps, on the other hand, the mechanical dilation of the smaller blood vessels is associated at a certain point with a sudden marked increase in permeability the effect of which dominates the picture for a time.

At all events, whatever this intermediate mechanism may be, it ultimately fails to provide the necessary differential, and thereafter the hemoglobin concentration progressively declines while the venous pressure progressively increases until death supervenes.

It thus appears that increasing venous pressure is the immediate cause of death. Wiggers and Katz [15] and Meek and Eyster [16] have shown that in "good hearts" a circulatory crisis of decompensation occurs when the pressure of blood in the atrium reaches 250 to 310 mm. of water. The venous pressure just before death for 2 of our 5 animals definitely fell within this range, and values for 2 of the remaining 3 at death rather closely approached it. In 1 of the 5 animals, on the other hand, the venous pressure at death was considerably less. It may be that this discrepancy was due to the fact that this animal did not have a "good heart" to begin with. At all events, Wiggers' experiments and ours are not exactly comparable. Apparently, increases in venous pressure were produced very rapidly in Wiggers' experiments, even though they were produced by infusions of saline solution, whereas in our experiments the increase in venous pressure was gradually built up

15. Wiggers, C. J., and Katz, L. N.: The Contour of the Ventricular Volume Curves Under Different Conditions, Am. J. Physiol. **58**:439-475, 1922.

16. Meek, W. J., and Eyster, J. A. E.: The Effect of Plethora and Variations in Venous Pressure on Diastolic Size and Output of the Heart, Am. J. Physiol. **61**:187-202, 1922.

during more than two hours. Thus the duration of the exposure to increased venous pressure may have weakened the hearts of certain of our animals to such a degree that they actually succumbed to a relatively low intra-atrial pressure.

We have been interested in the question whether at the time when the circulating blood volume is at its maximum the vascular system is actually dilated to its utmost physiologic capacity. That this is probably not true is suggested by the results shown in chart 4. This is a kymogram showing the effect of allowing animals to inhale amyl nitrite at intervals throughout a massive infusion of 1 per cent sodium chloride solution. The depressions in the blood pressure that consistently result from this procedure suggest that the vasodilator mechanism is still

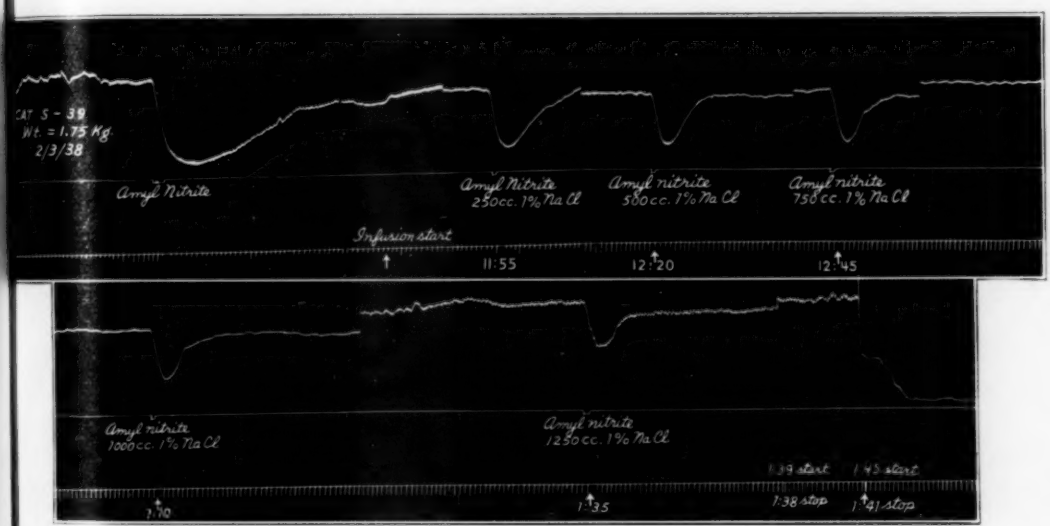

Chart 4.—Characteristic response to administration of amyl nitrite throughout a lethal infusion of 1 per cent saline solution.

active even up to about four minutes before death in an infusion which lasts nearly two hours. The drug, being in gaseous form, could not conveniently be given in measured doses, and for this reason the responses cannot be considered as quantitatively comparable. The fact, however, that all of the inhalations during the actual infusion showed responses of approximately the same magnitude somewhat suggests that vasodilator mechanisms play no more than a minor role in the accommodation of the circulatory system to increased volumes or, from another point of view, may be taken as evidence that there is little actual increase of blood volume to be accommodated.

Considering the evidence afforded by arterial pressure, venous pressure and blood volume and the apparent similarities of response evoked

by saline, dextrose and acacia infusions, we believe there can be little doubt that the cause of death induced by massive infusions of isotonic solutions of these substances is the same in all cases. The animals die as a result of circulatory failure. Terminally the respiratory center fails first, and directly thereafter the heart undergoes complete decompensation, with the values for blood volume and venous pressure at the maximum.

GROSS OBSERVATIONS AT AUTOPSY

In general, the gross observations at autopsy on a cat dying from massive infusions of 5 per cent dextrose solution are closely similar to those shown by an animal dying from a massive infusion of 1 per cent saline solution. The following is a typical protocol recording all the features usually noted in the case of dextrose solutions.

External Examination.—There is distention of the abdomen, but little edema either of the extremities or of the body wall. No other features of interest are seen.

Peritoneal Cavity.—When the peritoneal cavity is opened it is seen to be filled with clear serous fluid, which measures 70 cc. The stomach and intestine are both moderately edematous. The former contains 15 cc. of clear yellow bile-stained fluid. The latter contains 35 cc. of clear nonmucoid, nonbile-stained fluid. The large intestine presents a normal appearance externally and on being incised is found to contain a moderate amount of formed feces covered with mucus. The liver is perhaps slightly enlarged but is otherwise normal in color and general appearance. The gallbladder is pale, contracted and virtually empty. The pancreas, the retroperitoneal space and the adjacent spaces between the leaves of the mesentery present a remarkable appearance; a gelatinous edema pervades this area and has widely permeated the pancreas, so that the latter appears broken up into a series of lobulations, the fragmented organ being very pale.

The kidneys are somewhat enlarged and pale; their capsules are under tension, and when incision is made a small amount of clear serous fluid is discharged through the incision. The cut surface of these organs is pale and drips clear, colorless fluid. The spleen is normal in size and appearance.

Thoracic Cavity.—The pleural cavities together contain 10 cc. of clear serous fluid. The surfaces of the lungs are spotted diffusely with minute petechial hemorrhages. The upper lobes are pink, crepitant and apparently normal. The lower lobes are congested, dark bluish red and definitely edematous; clear, frothy fluid can be squeezed from their cut surfaces. The chambers of the heart are collapsed, but otherwise the organ is normal in appearance; the pericardium contains no extraordinary amount of fluid.

Cranial Cavity.—The cerebrum appears normal; the convolutions are well marked, and there are no evidences of either compression or shrinkage of the organ. Only a normal amount of cerebrospinal fluid is found.

As has been stated, the variations from normal seen in these animals are similar in many respects to those seen in animals succumbing to the effects of massive infusions of saline solution. The pancreatic and retroperitoneal gelatinous edema, which is the most remarkable anatomic feature at autopsy in both cases, is, however, definitely less spectacular after dextrose infusions. In both cases there

is considerable free colorless watery fluid in the peritoneal cavity—less after dextrose infusions, as might be expected. Pulmonary edema, present in both cases, is less marked after dextrose infusions. Gross evidence of cerebral edema is seen in neither, but most of the other tissues are pale and watery under both conditions. The characteristic differences are: (1) Buccal and nasal secretions are more copious in the case of saline infusions; (2) animals receiving such infusions show diarrhea, which is absent in the case of dextrose infusions (colonic contents are formed and almost normally inspissated); (3) the gall-bladder is distended and full after saline infusions, contracted and empty after dextrose infusions; and (4) the heart is full and dilated in the former case, empty and flabby in the latter. We have not observed in these experiments in which death was more or less suddenly produced the gross lesions described by Jacobs and Colwell [17] which apparently are seen after prolonged dextrose injections in dogs, namely, congestion of the serous membranes and meninges, hyperemia, swelling and softening of the hypophysis, pallor, enlargement and friability of the liver, congestion, gross hemorrhage and even frank gangrene of the pancreas.

The changes which we have observed apparently are not inconsistent with complete and relatively rapid return to normal, for if the infusion is stopped somewhat short of actual failure of the heart, some animals make an uneventful recovery within from twenty-four to thirty-six hours. If such animals are killed and autopsy is performed after five or six hours, most of the gross abnormalities are found to have abated. Except for the presence of some clear peritoneal fluid and a condition of the retroperitoneal tissues and the pancreas which is approximately midway between the intense edematous condition found at the end of the infusion and the normal appearance of these parts, there is little evidence of abnormality within the abdominal cavity. Within the thorax the pathologic changes of the lungs have entirely disappeared except at the extreme bases, and the heart appears normal.

At the end of about twenty-four hours the gross appearance of the contents of the abdominal and thoracic cavities may be normal.

INTRINSIC TOXICITY OF DEXTROSE

Although we believe that the foregoing is an accurate description of the cause of sudden death resulting from infusions of isotonic solutions of either dextrose or sodium chloride at rapid rates, we have reason for believing that if such infusions are interrupted just short of death the subsequent course of events may not be exactly the same with both solutions. Animals given infusions of just sublethal doses of saline

17. Jacobs, H. R., and Colwell, A. R.: Lesions in the Pancreas and in the Anterior Hypophysis with Fatal Acidosis Following Prolonged Intravenous Administration of Glucose (in Dogs), Am. J. Physiol. **116**:194-200, 1936.

solution recover without exception, and, as far as clinical indications go, their recovery is virtually complete within twenty-four hours. Such animals live indefinitely and show no complications or sequelae as far as can be clinically observed. Animals given infusions of just sublethal doses of dextrose solution, on the other hand, are quite as likely to die within a few hours as to live, and if they live they are likely to remain drowsy and depressed for a period varying from twenty-four to forty-eight hours. The depressed animals sometimes present peculiar clinical manifestations ranging all the way from a sort of general stupidity to muscular twitchings; the latter amount at times to mild tonic and clonic convulsions. In a single instance the animal's behavior was that characteristically seen after decerebration. In this case there were blindness, general muscular weakness (affecting particularly the hindlegs, though not to the extent of preventing the animal from standing) and a definite tendency to develop cataleptic postures, which were maintained for minutes at a time. Animals showing moderate depression usually recover and ultimately live indefinitely in an entirely normal condition. Those showing severe degrees of toxicity die after variable intervals.

Such convalescent peculiarities of animals infused with massive doses of 5 per cent dextrose solutions, which are never seen in animals infused with 1 per cent saline solutions, suggest that dextrose in the concentrations in which it occurs terminally as a result of such infusions is itself toxic. The terminal blood sugar levels of the animals with which we carried the infusion to actual death were determined and found to range generally above 2,000 mg. per hundred cubic centimeters of blood, the actual range for 6 animals being from 1,980 to 2,620 mg. On the other hand, in the case of survival experiments, because of the impossibility of predicting the exact moment at which death will occur it is necessary to estimate on the basis of clinical manifestations when the lethal point is approaching and stop the infusion just in advance of it. In such cases, of course, one does not have the guidance of blood pressure tracings, and the tendency is naturally to err in the direction of conservatism. As a matter of fact, estimations of the blood sugar at the point of cessation of infusion in our survival experiments show that 2,000 mg. per hundred cubic centimeters of blood has never been exceeded. From the research which has appeared to date on the subject of dextrose metabolism under conditions of artificial addition of dextrose to the circulation, it appears that dogs do not survive blood sugar levels of more than 2,000 mg. per hundred cubic centimeters for much more than two hours, for at this level disturbances of renal function appear and toxic manifestations are shown by unanesthetized animals.[18]

18. Wierzuchowski, M.: Overflow Diabetes and Toxic Phenomena Due to the Infusion of Glucose in Normal Dogs, J. Physiol. **87**:85P-86P, 1936.

CONCLUSIONS

Animals tolerate intravenous infusion of isotonic solutions of sodium chloride or dextrose in much larger quantities and at much higher rates of speed than seems to be generally appreciated. If animals (cats) are not allowed to fall victim to either of the two common varieties of accidental death, aspiration drowning following regurgitation or fatal intoxication with fever-producing contaminants of water, infusions of isotonic sodium chloride can usually be given at rates as high as 5.1 cc. per kilogram of body weight per minute without causing death or interfering with complete clinical recovery and indefinitely continued health. Isotonic dextrose solutions may be equally well tolerated at a somewhat decreased speed of injection and in a somewhat smaller total amount, but still in relatively huge doses, that is, at rates up to 4.2 cc. per kilogram of body weight per minute and in volumes up to 465 cc. per kilogram of body weight per minute.

When such total doses or rates of infusion are exceeded, death occurs from cardiac decompensation. The physiologic mechanisms of blood dilution, capillary filtration into the tissue spaces, urinary excretion and secretion into the peritoneal cavity and gastrointestinal tract act as efficient compensating mechanisms up to a certain point. Beyond this, however, the vascular load gradually produces a progressively increasing venous pressure which, when it attains a value somewhere between 150 and 250 mm. of water in the great veins draining into the right side of the heart causes acute cardiac decompensation and death. The respiratory center undergoes paralysis due to anoxia a few minutes before the terminal abrupt fall in blood pressure which signalizes cardiac failure.

Gross pathologic observations on animals dying suddenly from the effects of such massive infusions fail to show evidence of cerebral edema. Pulmonary edema, especially at the bases of the lungs, ranges from moderate to severe. The peritoneal cavity contains relatively large collections of clear serous fluid, though the pleural and pericardial cavities contain little secretion. Secretion into the gastrointestinal tract is voluminous in the case of saline solutions and relatively slight in the case of dextrose solutions. The retroperitoneal space and the pancreas show a gelatinous edema which is the most spectacular feature of the pathologic picture. None of these changes is inconsistent with complete clinical recovery of the animal and an indefinitely prolonged life thereafter; in about twenty-four hours all gross evidence of change has disappeared in animals which are allowed to survive.

Dextrose solutions infused at the concentration and at the rate reported produce a blood sugar level of some 2,000 mg. per hundred cubic centimeters. Apparently this level is a critical one, below which the

intrinsic toxicity of dextrose is not so likely to be acutely felt but above which specific lesions are rapidly produced which themselves are fatal. Because of the peculiarities of individual susceptibility there is probably about an equal chance that animals in which the blood sugar levels have been brought to such a value for short periods, though they may survive for a while, will die within a period varying from twelve to twenty-four hours. In the remaining animals, however, no change may occur which is inconsistent with complete clinical recovery. The failure of animals to tolerate as great a speed of injection or as large total quantities of dextrose as of saline solution for short periods is probably associated not so much with this phenomenon as with the fact that dextrose solutions do not undergo diffusion from the blood stream or elimination either by the kidney or the gastrointestinal tract with the same facility as do saline solutions.

OPERATIVE TREATMENT FOR BENIGN RECTAL STRICTURE (LYMPHOGRANULOMA VENEREUM)

PRELIMINARY REPORT

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It is generally conceded that the large majority of nonmalignant and nontraumatic strictures involving the rectum, especially those occurring in Negro women, are caused by lymphogranuloma venereum. Many articles have appeared in the medical literature describing this condition since Frei [1] introduced his intracutaneous test in 1925.

The causative agent is thought to be an ultramicroscopic virus transmitted during coitus, which after an incubation period of one week causes a transient, painless ulcerative lesion on the genitals. Two weeks later there is edema of the lymph nodes draining the initial lesion, associated with hyperplasia of the lymphoid tissues, fibrosis and abscess formation. These secondary manifestations vary with the sex of the patient and the location of the primary lesion. Martin and Bacon [2] in their detailed report of this condition stated:

> There exists a dense network of lymphatics in the external genitalia and anorectal region of both the male and female. Those of the prepuce and frenulum pass to the superficial inguinal nodes, whereas those from the glans sulcus coronarius and mucosa of the urethra drain into the deep subinguinal nodes. . . . Thus, the superficial, inguinal and the superficial and deep subinguinal nodes form an unbroken chain, the afferents of which pass mainly to the external iliac nodes. There also exists a minor network . . . which anastomose with those of the prostate, bladder and ano-rectal glands of Gerota.
>
> The lymphatics of the vulva and clitoris in the female are almost identical with those of the prepuce and glans in the male, since the network of the vulva drains for the most part into the superficial inguinal nodes, and those of the clitoris into the deep subinguinal nodes. There exist . . . two lymphatic plexuses in the vagina the collective vessels of which are arranged in three groups. The superior and middle groups drain the upper and middle thirds of the vagina and empty into the hypogastric glands and external iliac glands, whereas the inferior group

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From the Department of Surgery, the Medical College of Virginia.

1. Frei, W.: Eine neue Hautreaktion bei Lymphogranuloma inguinale, Klin. Wchnschr. **4**:2148-2149 (Nov.) 1925.

2. Martin, C. F., and Bacon, H. E.: Lymphogranuloma Inguinale or Lymphopathia Venerea, Internat. Clin. **4**:250-293 (Dec.) 1935.

drains into the anorectal glands of Gerota, into those of the promontory of the sacrum and the hypogastric glands. Because the lymphatic network represents an almost unbroken chain, it is not difficult to understand the manner in which the anorectal glands of Gerota located between the rectal fascia and the longitudinal muscle layer of the rectum and the superior hemorrhoidal glands situated in the mesorectum, can receive lymph from these portions of the vagina as well as the lower portion of the cervix.

Excellent illustrations of the lymphatics involved in lymphogranuloma venereum may be found in a recent article by Lee and Staley.[3]

In the female the first evidences of rectal dysfunction are usually proctitis and superficial ulceration involving the lower two thirds of the rectum. Lymph stasis in the rectal wall below the involved nodes then develops, with edema and secondary infection. Months or even years may elapse before the typical dense but friable annular stricture appears. Fibrosis continues, with narrowing of the lumen until almost complete intestinal obstruction results.

Women appear more prone to systemic reaction than do men. Abdominal pain, weakness, irregular fever and pain in the joints often appear early. Nausea and vomiting occasionally occur. A marked secondary anemia is a rather constant late finding, and amyloid changes in the kidney are not infrequent. Several of my patients have shown a definite psychotic reaction.

The statement is frequently made that lymphogranuloma venereum is a relatively innocuous condition and that radical procedures are not justifiable in the average case. This is not true of the cases observed in the Hospital Division of the Medical College of Virginia. The patients are anemic and cachectic, and many have been semi-invalids for years. Those in whom the condition is of long standing have various degrees of cardiovascular-renal disease. They do not, as a rule, come to the hospital until the onset of obstructive symptoms. Secondary infection is always present, and perirectal abscess and rectal fistulas are frequent complications. While the lesion is usually located in the middle and the lower portion of the rectum, an occasional case is encountered in which the upper portion of the rectum and the sigmoid flexure and even that part of the small intestine which is contained in the pelvis are involved by direct extension. Extensive ulceration may be present in the rectum, and cases have been reported of spontaneous perforation followed by generalized peritonitis. Simple dilation of the stricture or excision of tissue for microscopic examination sometimes results in peritonitis and death. Practically every large series of cases has included fatalities

3. Lee, H., and Staley, R. W.: Inflammatory Strictures of the Rectum and Their Relation to Lymphogranuloma Inguinale, Ann. Surg. **100**:486-495 (Sept.) 1934.

from this cause. I recently observed a case in which death occurred four days after gentle dilation of a stricture and removal of tissue for biopsy.

This hazard is due to two factors. The friable tissues involved tear when incautious dilation is done, and even gentle manipulation may rupture an abscess in the diseased wall of the rectum. In the majority

Method of obliterating the cul-de-sac and performing a "double-barreled" colostomy. The points marked a^1, a^2 and a^3 represent purse string sutures. (In recent operations only two pairs of purse string sutures have been used.) The point marked *b* denotes continuous suture which is used to close the defect between the posterior surface of the uterus and broad ligaments and the posterior parietal peritoneum and anterior surface of the sigmoid flexure. (In recent operations this suture has been placed at a lower level than is here depicted.) The point marked *c* denotes the point of division of the sigmoid flexure at the second stage of the operation.

of cases the stricture is located between 3 and 8 cm. above the mucocutaneous border, and if the rectal wall is torn anteriorly the cul-de-sac of Douglas may be entered. In the female the rectouterine excavation is only 5.5 cm. from the anal orifice. Any stricture in the female that requires the introduction of the index finger past the second joint in order to palpate its upper limits is potentially dangerous.

In order that local procedures may be carried out without danger of peritonitis the following operation was devised and has been successfully performed on 10 patients with proved lymphogranuloma venereum during the past eighteen months. This procedure, in brief, is obliteration of the cul-de-sac by chemical irritation and suturing, followed by a colostomy. The operation suggests the Moschcowitz [4] procedure for rectal prolapse in that the true pelvis is closed in both cases. However, the purpose of the operation is entirely different, and the method followed is also dissimilar.

The technic is as follows: Spinal anesthesia is induced, and the patient is placed in the Trendelenburg position. A paramedian incision on the left is made from the symphysis pubis to the umbilicus. The distal portion of the colon and the pelvic contents are inspected. Diseased tubes and ovaries are removed. The intestines are packed away from the operative field, and the parietal peritoneum of the false pelvis is protected by moist sheets. The peritoneum lining the cul-de-sac is then painted with one-half strength tincture of iodine. Especial care is taken that the iodine comes in contact only with the area that will subsequently be covered by sutures.

A series of purse string sutures of chromic catgut are placed in each fossa, lateral to the rectum. The sutures include the lateral wall of the rectum and the parietal peritoneum of the cul-de-sac. They are tied in pairs in order that the rectum may not be distorted. Two rows of purse string sutures placed about 1 inch (2.5 cm.) apart will obliterate the cul-de-sac. Finally, continuous suture, beginning and ending with a purse string closure, is used to approximate the posterior surface of the broad ligaments to the posterior parietal peritoneum and to close the defect between the anterior surface of the lower portion of the sigmoid flexure and the posterior surface of the uterus.

In the earlier operations a bilateral salpingectomy was done to avoid the possibility of later pregnancy. In recent cases this has been omitted, but care has been taken that the final row of sutures should be placed sufficiently low to avoid impingement on the tubes and ovaries or immobilization of the posterior surface of the uterus. The sutures include the pelvic fascia, but the ureters and the iliac and ovarian ves-

4. Moschcowitz, A. V.: The Pathogenesis, Anatomy and Cure of Prolapse of the Rectum, Surg., Gynec. & Obst. **15**:7-21 (July) 1912.

Summary of Cases from Feb. 15, 1937 to July 20, 1938

Summary of Cases from Feb. 15, 1937 to July 20, 1938

Patient	Sex	Age	Duration of Rectal Symptoms	Degree of Stricture	Frei Reaction	Formaldehyde Reaction	Wassermann Reaction	Associated Conditions	Date of Operation	Type of Operation	Comment
L. S.	F	29	8-9 yr.	++++	++++	—	Negative	Inguinal adenitis (hemoglobin 58%)	2/15/37	Obliteration of cul-de-sac; ligation of tubes; colostomy	7/8/38, stricture practically disappeared; slight hernia about colostomy; hemoglobin 75%
G. M.	F	25	5 yr.	++++	++	—	Negative	Inguinal adenitis (hemoglobin 70%)	7/14/37	Obliteration of cul-de-sac; bilateral salpingectomy; colostomy	
R. S.	F	35	3-4 yr.	++++	++++	—	Negative	Rectal fistula, Bartholin's abscess (hemoglobin 80%)	7/27/37	Obliteration of cul-de-sac; appendectomy; colostomy	Stricture relaxing; patient gained 16 pounds (7.3 Kg.); hot enemas and dilations
V. T.	F	69	19 yr. (?)	+++	++++	—	Negative	Senility; hemorrhoids; rectal abscess; fistula; inguinal adenitis (hemoglobin 60%)	9/25/37	Obliteration of cul-de-sac; oophorectomy, right; colostomy; transfusion	7/8/38, stricture diminishing; hot irrigations and dilations; colostomy closing
E. B.	F	25	5 yr.	++++	*	+	Negative	Rectal fistula (hemoglobin 47%)	10/1/37	Obliteration of cul-de-sac; appendectomy; colostomy	7/15/38, stricture diminishing; hot irrigations and dilations
G. F.	F	30	2 yr.	+++	++	+	Negative	Rectal stricture (hemoglobin 63%)	10/27/37	Obliteration of cul-de-sac; colostomy	7/15/38, stricture relaxed; patient gained 11 pounds (5 Kg.); hot irrigations and dilations
M. J.	F	30	8 yr.	++++	+++	+	++++	Hemorrhoids (hemoglobin 78%)	2/1/38	Obliteration of cul-de-sac; colostomy	5/25/38, plastic operation on colostomy opening 7/8/38, stricture relaxing; hot irrigations
E. J.	F	25	1 yr.	++++	*	—	Negative	Rectovaginal fistula (hemoglobin 60%)	2/8/38	Obliteration of cul-de-sac; colostomy	
L. W.	F	27	5 yr.	++	+++	+	Negative	Proctitis; hemorrhoids (hemoglobin 40%)	5/12/38	Obliteration of cul-de-sac; colostomy; transfusion	7/1/38, proctitis and stricture diminishing
W. M.	M	38	3 yr.	++	++++	+	Negative	Proctitis (hemoglobin 62%)	6/22/38	Obliteration of cul-de-sac; colostomy	Patient in hospital at time of this report

* Reaction positive but degree not recorded.

sels must not be injured. Care must be taken to avoid constriction or angulation of the lower portion of the sigmoid flexure, as otherwise a stricture may result at this level.

A "double-barreled" colostomy is then performed through a McBurney incision on the left. The loop of sigmoid flexure is supported by a glass rod passed through the mesentery, and the bowel is opened with the cautery several days later. Ten days after operation the bowel is completely divided, and the glass rod is removed. This separation may be left as a permanent colostomy opening, or the continuity of the bowel may later be restored extraperitoneally at a time depending on the subsequent course of the patient. The infection diminishes after diversion of the fecal current, and the proctitis usually disappears. The stricture softens and responds to dilation. The danger of peritonitis is obviated, and if necessary further local operative procedures, such as the Keller tunnel graft [5] or the Lockhart-Mummery and Lloyd-Davies [6] operation, may be carried out on any part of the rectum with safety.

All of the patients operated on in this series have recovered and have been benefited by the procedure. In 1 of the early cases a small ventral hernia developed at the site of the colostomy. In the later cases greater care has been taken in suturing the aponeurosis of the external oblique muscle through the defect in the mesosigmoid, and no hernia has occurred. In 2 cases the upper segment of the sigmoid flexure retracted beneath the level of the skin, and a plastic procedure was necessary to prevent stenosis of the proximal loop. At present the upper segment is brought out under less tension, and there have been no further strictures.

The statement has been made that the stricture will recur if the continuity of the bowel is restored and the fecal current again passes over the involved segment. I have not closed the colostomy opening in any of my cases and do not know whether the stricture will reform. At the time of this report the stricture in all cases is relaxing, and I feel that the safety afforded by this procedure has already justified its use should no further benefit be derived from obliteration of the cul-de-sac.

The present treatment for strictures due to lymphogranuloma venereum in the Hospital Division of the Medical College of Virginia is as follows:

On admission of the patient a careful rectal examination is made to determine the degree of stenosis, the location of the stricture and the

5. Keller, W. L.: Annular Stricture of the Rectum and Anus (Treatment by Tunnel Skin Graft), Am. J. Surg. **20**:28-32 (April) 1933.

6. Lockhart-Mummery, J. P., and Lloyd-Davies, O.: Operative Treatment of Fibrous Stricture of the Rectum, with Description of a New Technique, Brit. J. Surg. **23**:19-24 (July) 1935.

extent of fibrosis. If the stricture is within the danger zone and if the index finger cannot be passed without difficulty, further local procedures are deferred until they can be carried out in the operating room under direct vision. The patient is given a diet low in residue but high in vitamin content, and liquid petrolatum is given. A Frei test and a formaldehyde ("formol gel") determination are made. Despite the pathognomonic nature of such a stricture, a small amount of tissue is removed from the posterior wall of the stricture for diagnosis, as cases of carcinoma associated with lymphogranuloma venereum have been reported by Liccione [7] and others. In many cases the patient has been ill for years and is more fragile than she appears. Blood transfusions are given if the value for hemoglobin is less than 60 per cent.

I formerly used antimony and potassium tartrate and (later) fuadin in such cases, without noticeable benefit. Elliott therapy, diathermy and sulfanilamide have been tried, with indifferent success. Hot rectal irrigations and oral administration of potassium iodide appear to allay the discomfort and have given as good results as any other measure.

Several years ago I temporized with this condition and relied on frequent dilations, but the patients did not cooperate well, and the results were unsatisfactory. My tendency now is to obliterate the cul-de-sac and form a colostomy opening as soon as a definite stricture is present. If the proctitis is severe and the Frei test gives a positive result, I feel that a colostomy is frequently indicated before an actual stricture has formed.

The after-care is relatively simple. Rectal irrigations with hot saline solution are given during patient's stay in the hospital, and after his discharge he is instructed to irrigate the diseased segment of bowel by inserting the tip of the syringe into the lower stoma of the colostomy opening. He is directed to return every two weeks to the outpatient department for dilation of the stricture. I have found that the patient returns with greater regularity after the opening has been made than before operation. This is due to the fact that the dilations are less painful after diversion of the fecal current and also to the patient's desire to facilitate recovery in order that the colostomy opening may be closed as soon as possible.

SUMMARY

Ten patients with rectal stricture resulting from lymphogranuloma venereum have been treated by obliteration of the cul-de-sac and colostomy.

7. Liccione, W. T.: Venereal Stricture of the Rectum: Adenocarcinoma as Late Complication, Am. J. Surg. **31**:551-555 (March) 1936.

The closure of the cul-de-sac has permitted dilation of the stricture without danger of peritonitis, and the diversion of the fecal current has resulted in relaxation of the strictures.

If necessary, further operative procedures on the stricture may be carried out through the rectum with relative safety.

This is a preliminary report, for operation in the earliest case was done only eighteen months prior to the time of this report, and none of the colostomy openings has been closed.

Dr. Robert V. Terrell referred most of the patients in this series to the Hospital Division of the Medical College of Virginia and has followed them in the outpatient department since their discharge.

710 Medical Arts Building.

OCCURRENCE, DISTRIBUTION AND PATHOGENESIS OF SO-CALLED LIVER DEATH AND/OR THE HEPATORENAL SYNDROME

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INTRODUCTION

Coincident with the repeated calling of attention to the interrelation of the liver and the kidneys in the determination of fatal outcome of operations on the gallbladder and biliary tract, a diversity of opinion has developed regarding the so-called hyperpyrexia liver death and the hepatorenal syndrome. Indeed, by certain authors (Heuer and others) the statement has been made that in all the cases observed by them at autopsy other causes which could adequately account for the clinical phenomena and the fatal outcome were demonstrable. Other observers (Boyce, Boyce and McFetridge, Stanton, Connell and others) have stated the opinion that the condition is more common than the references in the literature seem to indicate.

In this communication I shall attempt to assemble all available experience, shall examine, correlate and evaluate all the available apparent and discoverable factors, shall attempt to establish the accuracy of the prevailing assumptions in regard to this syndrome and shall, finally, attempt to find the cause and mechanism of this biologic progression.

CLINICAL TYPES

Two distinctive clinical pictures have been described: (1) that in which the outstanding symptom is hyperpyrexia occurring immediately after operation and leading quickly to death and (2) that of delayed death, associated with the hepatorenal syndrome.

HYPERPYREXIA DEATH

Hyperpyrexia has in certain quarters been correlated with the concept of so-called liver death.

There is a wide disparity of opinion concerning the incidence and nature of postoperative high temperature death. The phenomenon is not confined entirely to operative cases of disease of the liver and the biliary tract. For instance:

Crisp reported a case observed at the Mayo Clinic, in which "high temperature death" followed resection of the rectum for malignant tumor. There was no demonstrable evidence of peritonitis at this early stage, and the observers eliminated the possibility of surgical shock; there was marked evidence of extreme toxicity.

Since 1931 Connell has changed his opinion and in 1934 he reported 3 interval appendectomies, 1 laparotomy for ovarian cyst and 1 hysterectomy, after all of which high temperature death occurred. DeCourcy in 1937 reported 2 operations which were followed by high temperature death; 1 was a colostomy and the other a hysterectomy.

Boyce and McFetridge reported the case of a Negress on whom a resection of the cecum was done for acute typhlitis. The patient died within seventy-two hours, in hyperpyrexia. The nonprotein nitrogen content of the blood was 72 mg. per hundred cubic centimeters, in contrast to a preoperative level of 29 mg. Postmortem examination eliminated the presence of peritonitis or other surgical complication and showed hepatorenal changes typical of the hepatorenal syndrome. The same authors reported a second case, in which these clinical and anatomic changes were observed in association with carcinoma of the pancreas with metastases in the liver.

In my own experience with intestinal obstruction and especially with the operative release of a comparatively old intestinal obstruction (obstruction of forty-eight to seventy-two hours' duration) I have seen quick death associated with immediate postoperative hyperpyrexia on a number of occasions. For instance:

A child aged 9 months was admitted to the hospital with a typical picture of acute intestinal obstruction of approximately twenty-four hours' duration, due to

an acute intussusception. The child was immediately operated on, and during the operation the intussusception was easily reduced. The entire operation took about ten minutes. During the next eighteen hours the temperature rose to above 106 F.; tremendously toxic symptoms developed, and the child died. Postmortem examination showed negligible changes in the liver and some slight degenerative changes in the kidney. There was no time for chemical, bacteriologic or other laboratory studies before death occurred.

Cases of liver death are especially disconcerting, as with other types of disease one usually deals with very sick persons or with those requiring the severer types of operation, in which, so to speak, almost anything can happen. In these cases one begins usually with a patient who shows no signs of jaundice and is in good condition. The problem is relatively simple, and operation usually proceeds without any alarming occurrence. Then comes an immediate and progressive rise of temperature; disturbances of the sensorium quickly pass on to lethargy and coma; signs of excessive nervous irritability (carphologia and subsultus tendinum) appear; the patient is obviously very sick and then moribund, and death occurs within from twenty-four to forty-eight hours.

At postmortem examination one is disappointed at the anatomic observations. The hepatic cells show signs of disorganization or beginning destruction; occasionally the kidney shows some congestion, and rarely similar degenerative changes are seen in the renal cells. As far as I know, no bacteriologic studies have been reported; but in my own experience blood culture in such cases has frequently been negative. Nevertheless, it is not possible to brush aside the question of infection as the true cause of death.

The explanation of the clinical phenomena is especially difficult when one compares such a case with a case of postoperative acute cholangitis. Many patients for whom acute cholangitis is a new postoperative condition or an extension and exaggeration of a preceding lesion show high fever and marked toxicity immediately after operation. Death within twenty-four to thirty-six hours after operation is common. So far the resemblance of the clinical manifestations is exact; and if one were limited to this information, it would be hard to classify postoperative cholangitis anywhere but with hepatorenal disease. In the presence of acute cholangitis, however, blood culture is frequently positive, the pathologic picture in the liver differs in that acute inflammatory foci are present around the ducts, as opposed to degeneration of the central hepatic cells, and abscesses are common. It becomes apparent, then, that no matter what the clinical manifestations may be, the lesions are sharply divorced even though both are necessarily within the liver.

Another disturbing element in the concept of liver death is the fact that in many cases in which symptoms suggestive of liver death were present before death, postmortem examination revealed exclusive or

additional causes entirely competent to produce death with high temperature; commonly the cause was found to be a subphrenic peritonitis or abscess which had escaped diagnosis. Touroff has reported a series of such cases.

It is instructive to compare the phenomena in cases of liver death with similar phenomena in those of outstanding infection:

A young man was admitted to the hospital with the diagnosis of "chronic appendicitis," and appendectomy was done. During the next thirty-six hours the temperature rose to well over 106 F.; the patient showed marked signs of toxicity, and death occurred. Postmortem examination showed peritonitis, distinctive but yet in an early stage of development, and there were inconspicuous changes in the hepatic and renal cells.

Another young man was admitted with chronic osteomyelitis of the femur, and osteotomy was done. Prior to operation there was no fever, and there was no reason to think that bacteremia was present. Nevertheless, operation was followed immediately by a progressive rise in temperature, by increasing signs of general infection, by a growth of bacteria in the blood culture and by death within seventy-two hours. Postmortem examination showed the usual changes incident to a general infection but no special morphologic changes in the liver or the kidney.

Almost any surgeon of experience can duplicate experiences of this kind. Many experiences have shown that infection can reproduce clinical pictures almost exactly similar to those associated with liver death. I do not believe, however, that any physician of experience would say that in the cases just described or in any case of similar involvement the outcome was liver death.

HEPATORENAL SYNDROME

Patients with the delayed hepatorenal syndrome show a clinical picture which is fairly characteristic. The manifestations develop slowly. In a few cases the symptoms are mild and consist in increasing mental lethargy, gastrointestinal symptoms and diminished output of urine. There may be a variable degree of retention of nitrogenous bodies in the blood stream. Under the influence of the introduction of large amounts of fluids containing sugar and salt and occasionally of whole blood, the picture quickly rights itself, the laboratory findings return to normal and the patient recovers. It is difficult to determine how often this clinical picture develops, as unless one is on the watch for it the symptoms are likely to escape notice among the clinical phenomena which commonly follow serious abdominal operations.

In the most severe grade of disturbance there is no regression. The clinical subjective and objective symptoms increase in severity; the lethargy passes into coma; the gastrointestinal symptoms become more marked; the output of fluid from the kidneys steadily diminishes until in some cases there is virtual suppression of urine; carphologia, subsultus tendinum and occasionally convulsions appear, and death follows

shortly. In such cases jaundice is a common objective symptom. It is likely to appear in cases in which the phenomenon has not previously been present. In many cases, especially if the condition is severe, intestinal or other hemorrhage is described as an important symptom.

Between these extremes all grades of disturbance occur. In most cases the condition progresses quickly to a fatal termination; a few patients recover. The essential discoverable factors which appear to enter into the formation of the hepatorenal syndrome are degeneration of the hepatic cells and similar degeneration of the renal tubular epithelium. In no case is there any other satisfactory explanation for the hepatorenal syndrome and/or symptoms or for the fatal issue.

The hepatic parenchyma shows the following changes: About the central veins the hepatic cells show some shrinkage and cytoplasmic granulation. Between many of the cells of the lobule the biliary canaliculi and capillaries are plugged with pigmented material. Various degrees of necrotic change are observed in the hepatic cells, especially in those of the inner central portion of the lobule of the liver and about the larger bile ducts. The stellate cells of Kupffer are swollen and seem to show increased activity.

Helwig and Orr described accurately the anatomic changes in cases of trauma. There are large areas of hemorrhage in which no viable hepatic cells are present. Amorphous shadows, staining with the typical outline of hepatic cells, are found in masses in the hemorrhagic areas. The destroyed areas in the livers of patients who live long enough show evidences of attempted healing by scar tissue and of reformation of biliary canaliculi. Peripheral to the destroyed areas and surrounding the reparative areas the liver resembles that seen in cases in which no trauma has occurred.

Helwig and Orr emphasized resemblances seen in this anatomic picture to that observed in the presence of eclampsia.

The following changes are found in the kidneys: In the cortex, the convoluted tubules and the loops of Henle show extensive parenchymatous degeneration. Many tubules contain only two or three recognizable nuclei which are pale and hazy and are apparently undergoing lysis. Some tubules seem to have undergone complete necrosis. The epithelial cells of the differentiated tubules are frequently pigmented with fine greenish granules. The epithelium lining Bowman's capsule is swollen, and red cells are scattered about, surrounding the capillary tufts. In the capillary loops the endothelium is swollen, and a few polymorphonuclear leukocytes are scattered in the capillary channels. Cloudy swelling, granular, albuminous precipitate and pale casts are seen in the collecting tubules. Some attempts at regeneration of the renal epithelium are observed. In cases of trauma evidences of hemorrhage

and of the results of hemorrhage abound. These changes are surely related to the original trauma and not to the regenerative changes.

Hepatorenal lesions and/or symptoms are found under many diverse conditions in clinical medicine, and a careful factual examination of all of them is the physician's first problem. A summary of all the conditions in which hepatorenal lesions and/or symptoms have been found and described follows.

I. CLINICAL INCIDENCE OF HEPATORENAL SYNDROME AND/OR LESIONS AS RELATED TO SPECIFIC ILLNESSES OR GROUPS OF ILLNESSES AND TO ABNORMAL PHYSIOLOGIC STATES, CONDITIONS, ETC.

INCIDENCE IN RELATION TO DISEASE OR INJURY OF THE LIVER AND THE BILIARY TRACT

1. Disease of the biliary tract without jaundice, is almost always associated with cholelithiasis and occurs usually in patients over 40 years of age and more or less obese. Most of the patients, in spite of any coincident and/or associated cardiac and/or metabolic disturbances (hypertension, myocarditis, disease of the coronary artery or diabetes) are satisfactory operative risks, and operation is undertaken with no trepidation. The following three factors are elicitable in such cases: a lesion of the biliary tract (calculus and/or infective cholecystitis), postmortem evidence of degeneration of hepatic cells and postmortem signs of renal tubular degeneration.

2. With some patients the disease described in the foregoing paragraph is associated with a pancreatic factor, evidenced by a thickening of the head of the pancreas and sometimes by enlargement of the lymph glands which normally drain the pancreas. Heyd and also Boyce and McFetridge have called attention to this condition.

3. Obstructive jaundice of nontraumatic origin is commonly associated with disease in the biliary tract, most frequently brought about by cholelithiasis and profoundly aided by infection extending upward in the biliary tree. The one additional factor appearing in this disease, which precedes the development of the hepatorenal syndrome, is jaundice.

4. Similar conditions prevail when the obstruction is due to malignant growths, which occur most frequently at the papilla of Vater and the head of the pancreas and less frequently at various sites of the larger biliary ducts proximal to the papilla of Vater. Here, however, a new factor is introduced, namely the malignant growth; and in the light of present knowledge, it must be assumed that the cause of death can be one of two. In some cases death seems to be due to the same factors and events as in cases of obstructive jaundice; in the larger proportion,

however, the mechanism of death seems to be no different from that of death caused by malignant tumor in other parts of the body in which the hepatorenal factor is not present.

Conditions similar to those described in the foregoing sections have occurred after various operations on the biliary apparatus as well as when no operation has been performed.

5. In 1927 Furtwaengler reported a case from Clairmont's clinic in Zurich, Switzerland. The patient was a 22 year old woman who had been hurt in an automobile accident. A crushing injury of the liver was present. Jaundice did not develop. A clinical picture exactly similar to that usually seen when the hepatorenal syndrome is present followed, and death occurred three days later. Postmortem examination showed bilateral necrosis of the renal cortex in addition to the hepatic destruction. The series of cases of fatal disease of the biliary tract following operation collected by Stanton in 1930 included 1 in which the involvement was similar in all respects to that described by Furtwaengler.

6. In 1932 Helwig and Orr reported the case of a 15 year old boy who after traumatic pulpification of the liver showed extreme jaundice, diffuse hemorrhages in the serous cavities, scantiness of the urine and an increase in the nitrogenous elements of the blood, especially in creatinine. The typical hepatorenal syndrome developed. The patient lived eleven days. Postmortem examination showed, in addition to the destruction of hepatic cells, extreme degeneration and destruction of the renal tubular epithelium.

A picture similar in all respects to that in the cases of Helwig and Orr and of Furtwaengler was also described in 1935 by Boyce and McFetridge, from the Charity Hospital in New Orleans. Their experience included 6 cases, in some of which operation was performed.

The conditions described in the two sections immediately foregoing present the additional factors of a crushing injury of the liver and of pulpification of hepatic cells and tissue. Compare these data with those presented in the section on the effects of autolysis of tissue, which follows.

INCIDENCE IN RELATION TO OPERATIONS FOR OTHER CONDITIONS

In addition to such cases as those previously described, the literature contains a number of reports of cases in which the hepatorenal syndrome followed abdominal and other operations in which the liver and biliary tract were not primarily involved. For instance, Schutz, Helwig and Kuhn reported a group of 6 cases, in 1 of which the syndrome developed eleven weeks after an operation for carcinoma of the breast; they mentioned also a case reported by LeNoir and his associates, in which, after an operation for gastric ulcer, similar symptoms developed and the patient died. Other cases were referred to elsewhere in their communication.

INCIDENCE IN RELATION TO CONDITIONS ORIGINATING OUTSIDE THE LIVER OR BILIARY TRACT

Symptoms similar in all respects to those composing the hepatorenal syndrome are known to develop as a result of other conditions which have nothing in common with hepatic disease primarily and in the absence of any such conditions of the liver and biliary tract as have been described. The clinical, pathologic and anatomic study made by Rindone of 60 patients with complaints referable to the right side of the abdomen showed that the liver is always involved in the "right abdominal syndrome," whether simple or complicated. The involvement is inflammatory and degenerative, and the amount of damage is proportional to the severity of the symptoms. Rindone expressed the opinion that the anatomic changes result from toxic or bacterial products absorbed through the portal vein. These findings and Rindone's opinion were confirmed by Bombi, who studied this relation with special reference to the chronic forms of appendicitis. The syndrome may be associated with such widely diversified conditions as drug and chemical poisoning, thyrotoxicosis, pregnancy and intestinal obstruction. Indeed, Rowe, studying nearly 4,000 cases of various diseases, found the incidence of hepatic involvement, even including figures which he considered to be "heavily overweighted," to be approximately 10.91 per cent.

The following is a summary and description of these conditions:

1. *Toxic Effects of Drugs and Chemicals.*—A. A large number of drugs and chemicals are known to produce characteristic changes in the hepatic cell, leading to degeneration and necrosis. The list of these has been materially increased by addition of many newly synthesized drugs. The effect of anesthetic drugs (see section on anesthesia) is related to this syndrome in the effects on the hepatic cell. The most important of these drugs is chloroform. Hanner and Whipple showed experimentally that chloroform and phosphorus produce identical characteristic lesions in the liver. The case of apiol (parsley camphor) poisoning reported by Thiers, which terminated in death with the hepatorenal syndrome, seemed to be an instance of this sort. During the war anatomic pictures of necrosis of hepatic cells approaching the appearance of "acute yellow atrophy" of the liver were frequently observed as a result of the absorption of chemicals employed in the manufacture of explosives and other military supplies, especially trichlorethane and trinitrotoluene. Similar toxic effects were seen during prohibition, following the consumption of varnish removers, hair tonics, cleaning fluids and similar chemicals, which were taken for their intoxicating effects.

B. Similar effects on the hepatic cell have been reported as following the use of preparations containing cinchophen and some of its derivatives.

Among these Rabinowitz listed the following:

Agotan, Atophan, Quinophan, Phenylcinchoninic acid } (cinchophen)
Neocinchophen
Novatophan, Tolysin } (neocinchophen)
Atophanyl (sodium cinchophen combined with sodium salicylate and procaine hydrochloride)
Diiodoatophan, Biloptin } (a combination of iodine and cinchophen)
Oxyliodide (a preparation of cinchophen hydroiodide)
Phenoquam (a cinchophen preparation)
Leucotropin (a compound of methenamine and cinchophen)
Atrophan-urotropin (a combination of cinchophen and methenamine)
Fantan (a urethrane-cinchophen compound)
Iriphan (a strontium salt of cinchophen)
Weldona (a compound which contains, or has contained, cinchophen)
Farastan (monoiodocinchophen)
Atoquinol (allylphenylcinchonic ester)

Rabinowitz reported from Kessel's service at the Mount Sinai Hospital the case of a woman aged 51, who for arthritis, nasopharyngitis, infected tonsils and obesity had undergone a tonsillectomy in March 1929. The operation was followed by prolonged administration of sodium salicylate, iodides and cinchophen. After four weeks the patient was bedridden and jaundiced. She became comatose and more deeply jaundiced; pitting edema of the ankles was observed, and the liver felt small to percussion. A provisional diagnosis of acute yellow atrophy of the liver was made. The patient died. Diagnosis at autopsy was subacute yellow atrophy of the liver; jaundice; edema of the ankles; parenchymatous degeneration of the heart and kidneys; tracheitis and bronchitis; obesity, and hemorrhages in the skin and mucous membranes of the intestine, the trachea and the bronchi.

Cabot stated that in cases of cinchophen poisoning observed at the Massachusetts General Hospital "there were distinct degenerative changes in the tubular epithelium of the kidneys, though similar changes were more marked in the liver."

In the cases reported by Palmer and associates there were outstanding pictures of acute yellow atrophy (toxic necrosis) of the liver. Palmer has given me the incidence and character of the accompanying renal lesions, as classified by his house officer, Lyman:

	Cases
Acute parenchymatous degeneration	9
Chronic nephritis with acute degeneration	1
Acute toxic tubular nephritis	1
Parenchymatous degeneration with biliary pigmentation	2
Bile staining	3
Chronic passive congestion	2
Glomerulonephritis	1
Fatty degeneration	2
Arteriosclerotic scarring	2
No change noted	1
Total	21

This summary gives a good view of the extent of the tubular and parenchymatous renal degeneration which accompany the hepatic lesions in cases of cinchophen poisoning.

C. Another of the newer drugs is germanin. Veiel introduced it in 1931, in the treatment of pemphigus vulgaris. Autopsy reports either on human beings or on experimental animals treated with germanin are few and incomplete. Nevertheless, there is evidence of a tendency to hemorrhage, to the formation of areas of focal necrosis with fatty changes in the liver and to constant and striking epithelial degeneration with necrosis in the renal tubules.

D. Identical pathologic changes in the liver and kidneys follow the use of peptone, histamine and albumose. The work of Hofbauer suggested that these substances might have some relation to the "eclamptic" conditions of pregnancy; the existence of any such association was disproved, however, by Stander. According to the latter author, these substances produce degenerative changes in the liver, involving the greater part of the lobule and leaving free only a rim of normal cells about the periphery. The condition is, therefore, strictly speaking, central necrosis, whereas in the presence of eclampsia there is typical peripheral necrosis.

E. A large group of compounds has developed since the introduction of arsphenamine for the treatment of syphilitic conditions. Extensive lesions occur, approaching those of acute yellow atrophy of the liver. Best has collected over 400 cases.

Heyd has reported 1 case in which death occurred during coma from hepatic degeneration, with "intense nonobstructive" jaundice which he attributed to arsenical poisoning.

F. The newest drugs to produce this syndrome are sulfanilamide and an elixir of it made with diethylene glycol. Studies were made under the auspices of the American Medical Association as a consequence of reports of a number of fatalities following the use of this drug. Microscopically the most marked changes have been observed by Cannon in the kidneys and liver. The epithelium of the convoluted tubules shows intense hydropic degeneration, sufficient to block the lumen and to alter the normal structure. In some animals necrosis caused disappearance of the cells. The collecting tubules are relatively unchanged. In addition, the glomerular tufts show shrinkage, although the blood channels are still patent and full of blood. The general picture is that of severe chemical nephrosis. The hepatic cells show similar changes, with the bulk of the lesion around the central veins; the necrosis is not severe, and leukocytic infiltration is minimal. The changes are not caused by sulfanilamide alone. Kesten, Mulinos and Pomerantz showed that the lesions may be produced by diethylene glycol alone.

2. *Toxemia of Pregnancy.*—The normal anatomic changes in the liver produced by pregnancy are: (1) increase in the weight of the organ (only in animals) and functional hypertrophy, which does not occur in the kidneys; (2) decrease in glycogen, which is not constant, and (3) fatty infiltration of the central lobes of the liver (venous and biliary stasis). Formerly the latter two changes were thought to indicate insufficiency, but today this theory is difficult to reconcile with the view that they are physiologic processes.

In pathologic states complicating pregnancy a number of clinical entities have been gathered under the generic term of "eclamptic states," "preeclamptic states" or "toxemia of pregnancy." They occur either early or late in pregnancy; clinically they are characterized by pernicious vomiting, nervous and mental changes, anemia, epigastric pain and tenderness, hypertension, albuminuria, eylindruria, bilirubinemia, azotemia and convulsions.

Typical toxemic states ("eclamptic" or "preeclamptic" states) may follow glomerulonephritis, pyelitis, pyelonephritis or vascular hypertension, which in turn may be complicated by secondary nephritis. Practically speaking, these are examples of "nephritis" complicating pregnancy or of a primary cardiovascular lesion in which "nephritis" supervenes and complicates the pregnancy. This aspect of the problem is of no present concern except in the similarities of the conditions to the hepatorenal syndrome.

Pathologic lesions in the liver, as well as functional impairments, are found only irregularly during pregnancy and seem unrelated to the previously described renal and cardiovascular conditions. According to Heynemann, mild pathologic conditions of the liver occurring during pregnancy are usually of an easily reversible nature, and possibly their incidence exceeds that of renal and cardiovascular lesions. Clinically they are apt to appear as cases of hyperemesis, infection, catarrhal jaundice (various forms of cholangitis) and intestinal intoxication. The transition of any mild condition into a severe one is relatively and actually rare, according to Heynemann. Severe disease of the liver approaches more and more, in accordance with its severity, "the picture of acute yellow atrophy of the liver."

Pathologically, scattered areas of hepatic lobular necrosis appear with some frequency in a certain proportion of cases of pregnancy complicated by "toxemia." It is to be noted that in pregnant patients necrosis of the hepatic cells begins in the periphery of the lobule and increases progressively toward the center, whereas in nonpregnant patients presenting the hepatorenal syndrome the cellular necrosis begins in the center of the lobule and spreads toward its periphery. According to Peters: "The histological changes found in the tubules and glomeruli

of a large proportion of patients who die in the acute stages of toxemia, whether they had eclamptic seizures or not, have certain features which distinguish them from the lesions commonly found in acute nephritis." Bell and others expressed the belief that these differences are distinctive.

Metabolic changes during pregnancy, as evidenced by the study of the body fluids, are only suggestive. Although the sugar content of the blood during toxemia seldom falls to extremely low levels, some of the neurogenic symptoms have been ascribed to hypoglycemia. The nonprotein nitrogen content of the blood during the later months of pregnancy tends toward a low level; according to Peters, figures of 40 mg. per hundred cubic centimeters are commonly obtained at such a time. The urea nitrogen fraction should therefore not be interpreted as being only at the upper limits of normal but should be considered to indicate a considerable increase over normal for the pregnant woman.

There are enough clinical and anatomicopathologic manifestations in such conditions to make out an entity in which the liver and the kidneys play important parts. The resemblances are marked enough to make one take some of these toxemic states seriously into account in considering the hepatorenal syndrome.

The resemblance is accentuated by the following remarkable fact: In a certain proportion of cases eclamptic manifestations seem to be precipitated by labor and/or to follow immediately after delivery. This fact calls forcibly to mind the similar precipitation of manifestations which follows the release of obstruction in the biliary ducts or in the intestinal canal. It seems that a similar mechanism must function in each of these states (vide infra).

3. *Thyrotoxicosis.*—Hepatic lesions develop in a fair percentage of cases of hyperthyroidism and are followed by terminal renal changes which closely approximate the changes seen in the presence of the hepatorenal syndrome. As opposed to the finding that 10.91 per cent of 4,000 patients with various diseases showed hepatic lesions, Rowe found that hepatic disease follows hyperthyroidism in 22.44 per cent of cases. Lahey has commented on the close similarities between the hepatorenal syndrome observed in the presence of hyperthyroidism and that observed in the presence of primary pathologic conditions of the liver.

Numerous references to the association of icterus with thyrotoxicosis are found in the literature, beginning with that of Habershon in 1874 and continuing with those of Eger, Sutcliff, Eder, Sattler and others. Assmann distinguished one group of cases in which icterus resulted from cardiac insufficiency. In another group Assmann placed those cases, chiefly instances of severe general toxicosis and rapidly lethal outcome, in which the more severe conditions passed into acute yellow atrophy of the liver. Such conditions, he stated, were probably related etio-

logically to the preceding hyperthyroidism. Kerr and Rusk in 1922 reported a case of hyperthyroidism in which autopsy revealed what amounted to acute yellow atrophy of the liver, with marked parenchymatous changes in both the liver and the kidneys, and in a paper written in 1930 Kerr mentioned several cases of somewhat similar disease observed since then.

Boyce and McFetridge were impressed with the occurrence of the hepatorenal syndrome in association with disease of the thyroid gland. They emphasized the fact that the renal aspect had not been particularly stressed before their report. Weller also investigated this aspect of the problem extensively. At autopsy in 44 cases of hyperthyroidism he found evidence of marked hepatitis in 22 and of moderate hepatitis in 16, while in only 6 cases in the series was the liver normal. In a control series of cases of other conditions he noted precisely reverse conditions, that is, 30 cases in which there was no evidence of hepatic involvement, 13 of slight involvement and only 1 of marked involvement.

Lahey emphasized the fact that deaths associated with hyperthyroidism are chiefly liver deaths, as is proved by the terminal jaundice sometimes present, by the development of hyperpyrexia without infection and even before operation, and by the benefit, achieved with measures commonly used to combat hepatic damage, chiefly infusions of dextrose, forcing of fluids and transfusion.

Definite autopsic evidence of hepatic damage in thyroid disease has been furnished by a long list of observers and experimenters, including Weller, Kerr and Rusk, Hashimoto, Goodpasture, Beaver and Pemberton and Cameron and Karunaratne.

Experimental work along this line has been reported by Schryver (1905), Cramer and Krause, Parhon, Kuriyama, Fukui, Reinwein and Singer, Dresel, Goldner and Himmelweit, Simonds and Brandes, Hewitt, Hoskins, Farrant, Eger, Marine and Lenhart, Landau and Hashimoto. Numerous pathologic anatomic pictures have been described, showing the characteristic changes in the hepatic parenchyma. Bartels and Perkins' work on the hippuric acid test for hepatic function indicated that in many cases mild hepatic dysfunction or disturbance occurs, which without the use of this test might escape notice.

Indubitable proof was advanced experimentally by Hashimoto in 1921, his experiments being confirmed by Goodpasture in the following year. These workers fed albino rats with thyroid substance in an endeavor to reproduce the myocardial changes observed in human patients with disease of the thyroid, and they reproduced not only those changes but parenchymatous changes in the liver and in the convoluted tubules of the kidneys.

Maes, Boyce and McFetridge have called attention to the fact that a practical application of this knowledge has been emphasized by C. H. Frazier and his associates Brown and North, and by W. D. Frazier and Frieman, who have repeatedly pointed out the importance of intravenous administration of dextrose as a prophylactic measure against postoperative thyroid crisis and have furnished convincing statistical proof of their claims.

The first clinical observation of a condition which might properly be considered acute yellow atrophy in association with exophthalmic goiter was that of Kerr:

> The patient was a man aged 39, who first showed icterus on the fourteenth day after bilateral partial thyroid lobectomy for hyperthyroidism. Hepatic dulness was diminished, and bile was present in the urine. Death occurred two days later. At autopsy a diagnosis of "hyperplastic goiter with chronic interstitial strumitis" was established. The liver weighed 1,290 Gm. Its surface was coarsely granular and light brownish red. On section the normal structure was obscured, and the color was opaque reddish brown, with numerous scattered hemorrhagic blotches. On microscopic examination almost complete loss of the normal architecture was observed. In the periportal regions there was diffuse infiltration with lymphocytes and some plasma cells. Beyond (central to) these lymphocytic masses were areas showing the remains of necrotic hepatic cells, infiltrating lymphocytes and leukocytes and hemorrhage. The illustrations accompanying the description showed extensive necrosis of the parenchyma and fully justified the clinical diagnosis.

In the year after publication of the first report by Kerr, Raab and Terplan described a case of similar disease under the title "Basedow's Disease with Subacute Yellow Atrophy."

> Loss of weight, weakness, vomiting, rapid and sometimes irregular pulse and icterus had marked the clinical course. After death the liver weighed 1,160 Gm.; its consistency was reduced; the cut surface was diffusely yellow, with dark red areas, and the periportal and interacinar connective tissue stood out in relief. Microscopic examination showed extensive necrosis, lipoidosis, deposits of bile pigment and localized infiltrations of round cells and leukocytes in the necrotic areas. Fibroblastic proliferation and new-formed bile ducts gave evidence of attempted repair. The entire picture was that "which may properly be called subacute acute yellow atrophy of the liver."

Barker also has described atrophy and necrosis of the liver in connection with severe thyroid intoxication.

Mora has recently summed up the relation of thyrotoxicosis to pathologic conditions of the liver.

> Hepatic changes appear to be an integral part of the syndrome of thyrotoxicosis. This can be demonstrated clinically by the occurrence of icterus; physiologically, by the increasing evidence of altered hepatic dysfunction; experimentally, by the evidence of hepatic dysfunction following administration of thyroid substance and thyroxin; and morphologically by structural changes in the liver, varying in the acute stages from widespread degenerative, fatty and necrotizing processes to

the chronic lesion in which the changes are interlobular, irregularly distributed, involving the peripheral portions of the lobule and showing relatively more fibrosis and lymphatic infiltration than bile duct proliferation.

Weller informed me that there are no constant renal lesions in cases of thyrotoxicosis. "Many of the patients showed varying degrees of cloudy swelling and a few fatty changes, but these degenerative changes were no different in kind or degree from those seen in many other conditions." I do not agree with his assumption, in view of the facts which are gradually coming to light, that "no significance should be attached to them"; I am, rather, of the opinion that such changes indicate the general trend of renal lesions to accompany and/or follow degeneration of hepatic cells.

4. *Burns.*—The facts and phenomena and the pathologic anatomic changes following or accompanying death caused by the physical agency of heat (fire or boiling fluids) are as follows:

There is an immediate intense systemic disturbance, customarily termed "shock," the evidences of which (depression of all vital processes and low blood pressure) are too well known to warrant repetition. In some cases death results either immediately or within the first twelve hours; it may occur from small or mild burns as well as from those of larger extent. Hyperpyrexia is frequently present. In such cases Wilson and his co-workers were able to demonstrate infiltration of the liver and sometimes of the other organs with eosinophils. The clinical progression includes (*a*) vomiting, frequently of bloody material from erosions in the upper reaches of the alimentary tract, (*b*) drowsiness, passing into coma, (*c*) convulsions (in children) and (*d*) death.

This initial period is followed by a second period, lasting approximately five days, in which the clinical phenomena are those of some form of toxemia. Death also occurs frequently during this period. There have been a number of explanations for this toxemia:

a. Underhill and his associates have attributed it to an increased concentration of the blood, producing circulatory embarrassment.

b. Aldrich concluded that it is caused by bacterial infection in the burned area.

c. Clark and Cruickshank, in the report of the Mines Department in England, tended to show that both loss of fluid and infection operated in producing the toxemia.

d. The report of Wilson and his group denied the accuracy of these observations. These investigators showed that the concentration of fluid played no role, because the clinical signs were aggravated by the intravenous administration of fluids. They disproved the infectious theory by showing that cultures of the fluid which accumulates in the tissue below the burned area are commonly sterile; and in the few cases in

which it was possible to cultivate hemolytic streptococci from this fluid there were no signs of intoxication.

According to Keschner and Klemperer, there is a relatively high incidence of hepatic edema[1] in cases of death following burns; the experience of these two observers confirmed that of Eppinger.

The postmortem studies made by Agnes MacGregor (one of Wilson's group) showed characteristic changes in the liver in cases of death after burns. Areas of necrosis occurred in the centers of the lobules of the liver, with fatty degenerative changes. The tubules of the kidneys also showed degeneration, but the changes were less severe and less constant than were those in the liver. In some instances there were similar changes in the brain cells. In Weiskotten's cases hemorrhages occurred in the adrenal glands, and in Bardeen's cases there was so-called focal necrosis in the lymphatic tissue.

Wilson's group of investigators also observed 5 cases in which a form of "toxic" jaundice appeared, beginning about the fifth day after the burn occurred. The van den Bergh reaction was biphasic. There were no signs of bacterial infection in 2 of the cases.

In their studies Wilson and his group came to the conclusion that the hepatic changes associated with toxemia caused by burns are due to some toxin circulating in the blood and becoming concentrated in the liver. Experimentally, fluid from the burned area exhibited the same toxicity, and the animals died within twenty-four hours. Wilson expressed the belief that the toxins result from a slow autolytic change in the burned area and that possibly the action of the toxin is augmented by the products of bacterial infection. Curiously enough, the toxemia following burning of tissues is similar to the toxicity which has been observed to result from traumatization of tissues; and the augmentation by bacterial growth recalls the effect of symbiotic growth of bacteria in the presence of gas gangrene and in non-gas-producing forms of gangrene of the abdominal wall.

According to Duval, the clinical picture, the humoral changes and the local (cutaneous) and visceral lesions observed in the human being, when considered in the light of the results of animal experiments, lead to the conclusion that this phase of intoxication or toxemia is general and is due to the absorption of toxic products formed in the burned area. It is similar up to a certain point to the symptoms and lesions of toxemia produced by organic (diphtheria, typhoid) or chemical (pyridic bases)

1. Rössle maintained that parenchymal toxic edema of the liver is equivalent to acute diffuse serous hepatitis. It is interesting to note that he stressed its importance in association with the hepatic changes of thyrotoxicosis (see the foregoing material). Rössle's hypothesis is that in the presence of thyrotoxicosis a toxin is elaborated which acts particularly on the liver because of its detoxifying action.

products. Toxemia is autogenous after severe burns, the source being in the burned tissues. This acute autogenous intoxication in the first four days after a severe burn resembles greatly three other types of toxemia which physicians are beginning to understand, traumatic shock following severe injuries and the intoxications accompanying roentgen therapy or curietherapy. Observations of the physiologic-pathologic character of recent extensive burns and of the other forms of toxemia open up a new field of what might be termed diseases due to autogenous intoxication. In animals it has been found that repeated burns confer sensitization, which in turn confers a certain immunity or resistance toward burns.

Similarity to the hepatorenal syndrome is striking. There are, first, the occurrence of death with hyperpyrexia in the first few hours after the reception of the burn, corresponding to the so-called liver death and second, death as a delayed phenomenon with the clinical signs of toxemia, corresponding to the deferred death following the hepatorenal syndrome.

5. *Intestinal Obstruction.*—Simple blockage of the intestinal tract becomes increasingly important because of its secondary consequences. In clinical medicine one distinguishes the following:

A. High intestinal obstruction, clinically noted for causation of regurgitant vomiting, loss of large amounts of fluids (dehydration, anhydremia) and for disturbed physicochemical relations.

B. Low intestinal obstruction, clinically noted for causation of progressively increasing distention of the bowel and secondary vomiting.

The dangers are enormously increased because of vascular changes (strangulation ileus) and deepening toxemia. If the condition is neglected, necrotic areas form, perforation takes place and the patient dies of terminal peritonitis. There are marked differences between low and high obstruction.

The dominant characteristics of high obstruction are vomiting and loss of fluid. Physically, extreme grades of dehydration and anhydremia occur. The higher the point of obstruction and the closer its proximity to the stomach, the more rapidly depletion occurs. Chemically this has been shown (MacCallum, Vermilye, Leggett, Boas and Lintz; Hastings, Murray and Murray; Haden and Orr; Gamble and Ross; Hartmann and Smyth; Dragstedt and Ellis; Gamble and McIver, and Elman) to result in the development of a variable picture: the higher the location of the obstruction, the more rapidly the carbon dioxide content increases and the more constant and severe is the grade of alkalosis produced. Alkalosis occurs most prominently with pyloric obstructions. The lower the point of obstruction, in the upper reaches of the small intestine especially, the less constant and less severe is the alkalosis, so that often no significant change appears.

The dominant characteristics of low obstruction are distention and toxemia. The vomiting is slight or moderate, and the vomitus consists of matter from the small intestine. Azotemia is a constant finding, and in clinical practice it is my custom to estimate the gravity of the obstruction by the extent of azotemia.

In the presence of any obstruction both sets of factors are present to some extent. In many cases other recognizable factors are present. All of these can be enumerated as follows: ileus, vomiting, loss of fluids (dehydration, anhydremia), azotemia, autolysis of tissue and its effects, toxemias and preoperative or postoperative shock (and/or collapse). The picture is further complicated by the possible presence of chronic and acute cardiac disease with and without hypertension, diabetes, pneumonia or obesity.

Death occurs as a relatively sudden phenomenon with fever, oliguria, azotemia, and dehydration, or the clinical picture and the symptoms develop much more slowly. Hyperacute manifestations frequently develop with the sudden operative release of the obstruction; hyperpyrexia and toxemia are then dominant characteristics of the clinical picture, which terminates quickly in death.

The clinical similarities to the hepatorenal syndrome and to sudden death with hyperpyrexia (so-called liver death) are marked. I called attention to this similarity many years ago. In my own experience the hepatic lesions have been absent, have been immaterial or, the experiences having occurred before much interest was aroused in the hepatorenal syndrome, have not been particularly looked for or stressed.

In 1923 Rowntree and Brown made a report on a series of 11 cases of a form of toxemia which was associated with anatomic or physiologic stasis in the duodenum. The toxemia was characterized by the following rather definite clinical picture: (1) vomiting of large amounts of thin serous bile-stained fluid; (2) evidences of dehydration, a red florid complexion, a high hemoglobin value, low blood pressure and asthenia; (3) tetany-like manifestations; (4) features of superimposed uremia and (5) occasional evidences of shock. The blood showed (1) a low level of chloride, (2) a high carbon dioxide capacity and (3) a high level of urea and of creatinine. Urinalysis revealed the presence of albumin and casts. Studies of renal function showed high values for urea and creatinine and a decreased excretion of phenolsulfonphthalein. In 6 cases necropsy revealed nephrosis, with characteristic changes in the tubular epithelium, or diffuse nephritis. No hepatic lesions were described in this report.

Boyce and McFetridge expressed the belief

> that certain deaths in intestinal obstruction are exactly akin to such deaths after gallbladder surgery. The clinical manifestations are the same, extreme hyperpyrexia with oliguria or complete anuria if the patient happens to live

long enough; in intestinal obstruction he usually does not. If postmortem is done, there is an absence of all positive findings which could explain death, other than necrotic changes in the liver, associated with similar degenerative changes in the convoluted tubules of the kidneys if the patient has lived long enough.

Those authors explained these deaths on the basis of functional hepatic insufficiency, noted in 14 of their cases by clinical evidence, plus anatomic lesions in the liver and kidney, noted in 9 other cases. The postmortem changes were "typical."

Cole and Elman have interested themselves in this problem, and they have been able to reproduce such changes by experimental obstruction. They have proved their point by tests of hepatic function as well as by the histologic observations at necropsy.

The observations of Werelius, made in 1922, are extremely interesting. In commenting on the experimental work of Dragstedt and his associates, he pointed out that for drained and for undrained obstructed duodenal loops the results were exactly similar; but it was noted that about twenty-four hours after the loops were drained the biliary secretion stopped completely and was replaced by a clear mucoid substance or, at times, a reddish fluid. In every instance the test for bile gave negative results. The cessation of secretions of bile heralded the onset of untoward symptoms; from that time on the animal rapidly lost ground, and the fatal issue was not long delayed. Werelius drew the obvious conclusion that the stoppage of bile was of the gravest possible prognostic significance for every one of the 33 animals used. In 8 instances bile was drained directly from the gallbladder, and in the others it was drained through the duodenum. In every case stoppage of bile meant death. It is seemingly a pathognomonic prognostic sign in the presence of high intestinal obstruction.

The stoppage of bile undoubtedly indicates severe intrahepatic disturbance with possibly a complete standstill of hepatic activity—in other words, a complete hepatic insufficiency aptly termed by Werelius "ahepatism." There is no doubt that such a severe or complete hepatic insufficiency would be either the dominating cause or a most important factor in the lethal outcome.

Sudden Release of Obstruction.—Typical forms of obstruction to the outflow of the fluid content of a hollow excretory passageway are well known as regards the biliary, the urinary and the alimentary tract. During any form of toxemia of pregnancy the uterine contents act in a similar manner to the contents of the obstructed biliary, urinary or intestinal tracts, for the powerful reason that rapid emptying of the uterus relieves the abnormal condition; as such, toxemia of pregnancy becomes, also, a form of obstruction.

A curious antithesis exists in all cases of obstruction: trouble begins and develops because the obstruction is not relieved, and occasionally an

exaggerated form of the same abnormality and disability is precipitated when the obstruction is more or less suddenly relieved.

The earliest instance which Elman could find of death following close on the sudden release of intestinal obstruction was reported in 1887 by Schede. Similar cases were described by Briddon in 1893 and by J. B. Murphy in 1897; a recent example was reported by Heusser and Schär.

There is abundant evidence in the literature, as has already been indicated, to the effect that the hepatorenal syndrome and/or lesions develop in conditions of the liver and biliary tract for which operation of no kind has been done and especially in cases in which there has been no demonstrable spontaneous release of the obstruction. Contrariwise, the hepatorenal syndrome and/or lesions in a rather severe and overpowering form are seen clinically to develop so soon after the release of obstruction by operative means (that is, sudden release) as to make the conclusion inescapable that the syndrome has some definite relation to the suddenly produced static and/or physicochemical conditions which follow the release of the obstruction.

More or less sudden calculous obstruction in the urinary tract on one side is commonly followed by restrictions in the urinary secretion of the corresponding kidney up to the point of complete suppression of secretion in the given organ. In the presence of bilateral formation of stones similar disturbances of function may follow, and one considers operative release of the obstruction with concern. Usually operative release of an obstruction on one side in the presence of a bilateral lesion is followed immediately or reasonably soon by the reappearance of function up to the total normal functional capacity of the kidney at the given moment. Occasionally, however, a state of complete suppression of urine follows the operation, and the preoperative condition is suddenly intensified to the point of complete anuria; that is, all the manifestations of the obstructive state are suddenly exaggerated after release of the obstruction.

The effects of intestinal obstruction have already been discussed and are well known. Contrariwise, the operative release of intestinal obstruction is sometimes followed by exaggeration of the preceding clinical manifestations. Here, also, similar conclusions as to the relation of the release of the obstruction and the immediate exaggeration of the subjective and objective symptoms and laboratory findings are forced on one.

The phenomena surrounding toxemia of pregnancy have also been previously reviewed in this communication. With pregnancy, too, it is well known either (1) that the manifestations of the already existing toxemia may be markedly exaggerated or (2) that the patient may be precipitated into toxemia when the products of conception are rapidly

evacuated from the uterus. Again, similar conclusions in regard to the intestines are inescapable.

Interestingly and curiously enough, each variety of disturbance, with the exception of the urologic conditions, both during the stage of obstruction and subsequent to its release are symptomatically and anatomically related to the hepatorenal syndrome and/or lesions. The parallelism is exact with each variety of obstruction. Clinically one finds cases of hyperpyrexia and sudden death which recall quickly the so-called liver death and one also finds cases of delayed hepatorenal syndrome and/or lesions. All the factors which are found to occur with the latter are also present in cases of obstruction; and the cases of biliary disease do not differ in this regard from cases of intestinal obstruction or pregnancy. Degenerative changes typical of the lesions exhibited in the deferred hepatorenal syndrome are present in the hepatic cells and the convoluted tubules of the kidneys. If there is any difference, after the release of an obstruction the renal changes seem more dominant.

II. CLINICAL INCIDENCE OF THE HEPATORENAL SYNDROME AND/OR LESIONS AS RELATED TO JAUNDICE

In the previous part of this communication hepatorenal symptoms and/or lesions were discussed from the point of view of the various conditions in which jaundice is an important symptom at one time or another and in which the hepatorenal syndrome is likely to occur. It is of equally great advantage to examine the syndrome from the point of view of jaundice.

Jaundice of one form or another may occur at any stage of life, not excluding fetal existence. Patients of any age may show mild or severe forms, and it is not unusual for the mild varieties to pass over into the most severe forms under sufficiently provocative circumstances, sometimes as a slow insidious process and at other times with the dramatic suddenness of acute yellow atrophy of the liver. Extensive hepatic necrosis and concomitant renal degeneration can be found at most unexpected times, as witness the case of a stillborn boy, reported by Degener and Jaffe.

In approaching the subject from the point of view of jaundice, one notes the following groups of pathologic conditions:

1. *Essentially Surgical Conditions.*—Under this heading (previously discussed) come: (A) acute and chronic cholecystitis and cholelithiasis; (B) acute and chronic disease of the bile duct, with or without calculus formation, and (C) obstructions of the common duct.

2. *Infections.*—As long ago as 1914 Merklen differentiated a large group of "acute infective hepatorenal insufficiencies" which are caused

by simultaneous infection of both liver and kidneys. This large group of infections includes the following:

A. Bacteremia of various kinds: of the typhoid-colon bacillus type, of which the important example is typhoid fever; of the pneumococcic type, of which lobar pneumonia is the outstanding example; of the influenza type; and of the ordinary staphylococcic type.

B. Special forms of bacteremia (septicemia), of which infection by Bacterium tularense is a good example. Lee Foshay told me:

> At every autopsy I have attended there have been necrotic focal lesions with necrosis in the liver, and about one-half of the cases have shown similar lesions, usually much smaller, in the kidneys. After death from tularemic septicemia there are usually countless billions of foci of necrosis throughout the entire liver substance. These lesions look just like those produced by tularemic septicemia in rodents . . . foci of necrosis are observed in the kidneys of rodents in at least one-half of the deaths, perhaps in about the same frequency as they appear in humans.

C. Local bacterial infections, usually of the typhoid-colon bacillus type, of which the outstanding example is acute cholangitis. It is interesting to note that this is possibly the mechanism whereby postoperative infections eventually progress into acute yellow atrophy of the liver.

> In 1 of my own cases it was possible to demonstrate post mortem the origin of the disturbance in an infection in the larger terminal ducts of the biliary tract.

D. Spirochetal infections, of which the best examples are spirochetosis icterohaemorrhagica and syphilis.

> Fleckseder's 3 patients showed the typical symptoms of Weil's disease. The serum of 1 of the patients who recovered agglutinated Spirochaeta ictohaemorrhagiae in the titer of 1:1,000, and the symptoms included fever, severe hepatic impairment, jaundice, hemorrhagic diathesis and acute renal symptoms.

E. Undifferentiated infections by some form of "virus." It seems certain that many conditions now included in this group will eventually be classified elsewhere as soon as their cause is accurately established. For the present, this group includes some forms of so-called catarrhal jaundice (angiocholitis), especially of the epidemic variety.

3. *Various Forms of Poisoning or Intoxication.*—Under this heading (see the foregoing section) come:

A. Conditions due to pregnancy. B. Thyrotoxicosis. C. Poisoning by various anesthetic and other drugs and chemicals. These conditions have been previously discussed in this communication.

4. *Conditions in Which an Important or Predominating Pathologic Element Is Massive Destruction of Cellular Tissue,*—An outstanding example of this group is furnished by the cases of pulpification of the

liver reported by Furtwaengler and by Helwig and Orr. (See the section on disease or injury of the liver and the biliary tract and that on autolysis of tissue.)

5. *Jaundice Caused by Various Forms of Intoxication or Poisoning, in Which Hemolysis Is an Important Symptom.*—This represents a complex group, including blackwater fever and snakebite. The most characteristic form is chronic hemolytic icterus.

6. *Obscure and Undifferentiated Jaundice of Which the Cause Is Still Undetermined.*—This group includes intestinal infection and/or intoxication, of which examples are Buhl's disease and Winckel's disease.

With all these conditions both mild and severe jaundice appear. Not always is the hepatorenal syndrome to be clinically distinguished or anatomically proved. Nevertheless, from time to time the syndrome appears in association with conditions belonging to each of these groups, and in direct proportion to the frequency and extent to which the condition approaches the severe forms of hepatic degeneration and necrosis commonly grouped under the generic term of "acute yellow atrophy of the liver" the hepatorenal syndrome becomes more and more evident.

"Icterus gravis" is a general term for all forms of severe jaundice caused by degenerative, infective or autolytic changes in the liver and the kidneys. It thus includes acute necrosis of the liver, occurring as a complication of previous hepatic disease or of many of the various forms of jaundice in which the renal element seems distinctly subordinate to the hepatic lesions, and the large group of infective hepatorenal conditions in the presence of which liver and kidneys suffer concomitantly, simultaneously and equally from the same infectious cause.

7. *Acute Yellow Atrophy of the Liver.*—The ultimate state to which all the previously listed conditions may progress is acute yellow atrophy of the liver. The literature contains numerous references to the fact that at one time or another examples of this progression have occurred in association with all the conditions described.

A typical and a severe form of the hepatorenal syndrome are, almost of necessity, part and parcel of the clinical entity. At postmortem examination the extent of the degeneration and necrosis in both liver and kidney is of maximum grade. This should be expected in view of all of the facts hereinbefore outlined.

One cannot avoid the conclusion that acute yellow atrophy of the liver represents the end result of a variety of other pathologic conditions; that it may result from these various causes because of a sufficient impairment and weakening of the powers of resistance of the patient, produced by disease or by unaccustomed physiologic strain; that the lesions result from the action of poisons of various kinds; that all of these various causes produce necrotic and degenerative lesions, some-

times in the liver and sometimes in the liver and kidney, and that the degree, extent, magnitude and relative proportion of the hepatic and renal lesions, extending from those of least clinical importance to the maximum dramatic manifestations of acute yellow atrophy and hepatorenal insufficiency, are questions of the dosage of poison or toxin delivered in the neighborhood of the hepatic and renal cells.

III. INCIDENCE OF LESIONS IN THE LIVER AND KIDNEYS AND/OR OF SYMPTOMS OF THE HEPATORENAL SYNDROME AS RELATED TO ASSOCIATED AND/OR ACCOMPANYING FACTORS COMMON TO MANY OF THE HEREINBEFORE MENTIONED CONDITIONS

1. *Effect of High Temperatures per se.*—Postoperative high temperature death is not entirely new, and cases were reported and discussed in the literature by Gibson, Johnson and Brewer in 1900, by Crandon and Ehrenfried in 1912, by Moschcowitz in 1916, by Martin in 1928 and by Cutting in 1931. At the beginning such deaths (occasionally the patient recovered) were correlated with heatstroke, but in 1931 and 1934 Connell began to question the assumed relation and introduced the idea of associating hyperpyrexia death with demonstrable anatomic changes in the liver. Credit for popularization of this concept is due to Heyd. The literature now contains numerous references to the subject of high temperature or liver death.

Boyce and McFetridge called attention to the fact that in all of the conditions with which they have observed the hepatorenal syndrome the pathologic changes described as occurring in the liver and kidney were especially noted when hyperpyrexia existed. In most of their cases when the clinical course was typical the postmortem changes were also typical; necrotic changes were present in the liver and were or were not demonstrably followed by similar changes in the convoluted tubules of the kidneys, in direct proportion, as Boyce and McFetridge concluded, to the length of the interval before death. These observers suggested that similar deaths with high temperature, occurring in cases of appendicitis or kindred conditions, might well be included in this category.

For many years I have noticed that during the excessive heat of the summer months, several postoperative deaths occurred every year, the outstanding terminal manifestation being hyperpyrexia. Curiously enough, such cases have almost always been instances of disease of the liver, or the biliary tract, or of thyrotoxicosis. When I compared these cases with cases of similar involvement in which operation was performed during the winter, the fact impressed itself strongly on me, as well as on the other surgeons in the hospital, that the only differentiating

factor in the two groups was the terminal hyperpyrexia, and one could not escape the conviction that the excessive heat and humidity strongly contributed to the hyperpyrexia and the fatal outcome. Indeed, so strong is my conviction of this that during excessively hot and humid days, I, as well as many other surgeons in the hospitals with which I am connected, have stopped operating except in emergencies. Curiously enough, accidents are always to be encountered at the beginning of the "hot spells"; as soon as patients—and persons in general—have become accustomed to the heat and humidity, such deaths cease to occur, and matters return to the course to which one is accustomed in the colder periods. I have discussed this in detail because Boyce and McFetridge have not noted any increase in the number of hyperpyrexia deaths under the climatic conditions of New Orleans, and the obvious explanation is that their patients are accustomed to the heat and the humidity.

A. Pathologic Effects of Fever Therapy: Highly interesting and reliable data are now available as a result of the new fever therapy. By this form of therapy hyperpyrexia is mechanically produced by various heating machines, and extraneous factors are at a minimum and can be excluded by proper controls. Identical reactions are obtained whether fever is produced by hot baths, by use of a cabinet, by diathermy or by radiothermy; and the nonharmful (physiologic?) reactions have been summarized by Neymann and Osborne, Bierman and Fishberg and Hench, Slocumb and Popp. The temperatures produced have varied from approximately 106 to 113 F.

The report of Warren, Scott and Carpenter concerning the treatment of gonococcic infection by artificial fever in 283 cases brings out the fact that jaundice and severe nausea and vomiting developed in 15 cases. In 2 cases hematuria also appeared, continued for about one week and then disappeared, without sequelae. Such unlooked-for symptoms apparently occurred only during the warm months. In some cases the icteric index rose as high as 18 by the third day, and there was a concomitant rise in the nonprotein nitrogen content of the blood to double its normal value. The latter, however, returned to normal more quickly than the icteric index. The sugar content of the blood was usually unchanged. The chloride content of the serum remained at the lower limits of normal or dropped below, but returned to normal on administration of sodium chloride. The jaundice likewise responded favorably in from three to five days when the intake of carbohydrates as well as of saline solution was increased.

Stafford L. MacLean, of the Strong Memorial Hospital, of Rochester, N. Y., gave me the record of a case in which death followed thirty hours after a twenty-four hour fever treatment. There were definite evidences of dehydration, and he was "able to prove very

definitely that there is liver damage where the chloride has been restricted." Microscopically, "the areas of degeneration (i. e., in the liver) which suggest early necrosis appear as central in location, but the occasionally scattered peripheral involvement may indicate its extension. There are small foci of scattered polymorphonuclears in the areas mentioned." The kidneys showed "a moderate degree of cloudy swelling."

The harmful (pathologic) effects of artificially produced excessive temperature have been summarized by Hall and Wakefield, by Jacobsen and Hosoi, by Baldwin and Nelson, by Baldwin and Dondale, by Schereschewsky, by Mortimer and, most recently, by Hartman and Major. The usual autopsic observations, as summarized by Hall and Wakefield and by Hartman and Major, include: ventricles in systole; generalized venous congestion, most marked in the mucous membranes, the lungs and the liver; hemorrhage; degeneration, and cloudy swelling of the kidneys. Characteristic degeneration was described in the adrenal glands. In the 2 cases described by Hartman and Major "acute parenchymatous degeneration of liver and kidneys" was specifically mentioned. The parenchymatous degeneration in the livers of the experimental animals used by Baldwin and Nelson was situated in the peripheral portion of the lobule. According to Hartman and Major, the hemorrhages in the various organs are partially due to the administration of morphine and/or amytal.

B. Pathologic Effects of Heatstroke (Heat Exhaustion, Insolation, Sunstroke, Thermic Fever): Factual knowledge concerning the pathologic effects of fever therapy is corroborated by the effect of excessive atmospheric heat. It seems that various clinical pictures may appear, which commonly merge into one another in the same subject. The pathologic picture is bound up with the degree of external heat and the humidity of the atmosphere and with the factors of production and elimination of heat by the human body; the most important of these as regards the production of serious effects is the degree of atmospheric humidity; to a much less degree the lack of circulation of the atmospheric air is contributory.

According to McKenzie and LeCount, the most important post-morten pathologic observations include petechial hemorrhages of the mucous membranes and the skin; generalized passive hyperemia; edema of the various parenchymatous organs; hyperplasia of the spleen; cloudy swelling of the liver, the kidneys and the myocardium, and diminution of the yellow cortical material in the adrenal glands. According to Halliburton and Mott, the physicochemical mechanism of death from the hyperpyrexia of heat stroke is the coagulation of cellular globulin. This is the essential physical change which produces the cloudy swellings in the liver and kidneys.

2. *Effect of the Various Forms of Anesthesia.*—For all patients operated on, the factor of anesthesia has always entered into the problem. The effect of the anesthetic depends on the kind and quantity of the agent employed and on the extent of hepatic damage that may be already present. Gagliardi's studies on the function of the liver by means of the bengal rose test and by estimations of the degree of bilirubinemia show that in a patient with a normal liver anesthesia and surgical trauma induce a transient hepatic insufficiency, which is more or less intense depending on the type of anesthesia and on the nature of the operation. In patients with preexisting latent or demonstrated insufficiency of the liver the condition is aggravated by the anesthesia and the surgical trauma.

Stander has shown, in animals, the effect of anesthesia on the constituents of the blood and on the histologic composition of the different organs. The effects on constituents of the blood were similar for the various inhalation anesthetics and were as follows:

A. Lowering of the carbon dioxide–combining power.

B. Hyperglycemia.

C. Increase in lactic acid.

D. Slight increase in uric acid.

E. Slight increase in inorganic phosphorus.

F. No disturbance or little disturbance of the nonprotein and the urea nitrogen.

According to Stander, this blood picture is almost identical with that observed in association with eclampsia, and the anesthetics produce pronounced hepatic lesions as well as changes in the kidneys.

The work of Rosenthal, Bourne and others, chiefly with dye tests, has shown that ether causes a definite although transitory impairment of hepatic function, rarely lasting longer than twenty-four hours, while Colunumal and Ascoli, Kehr, von Haberer and Stahler, Wilensky and others have pointed out that the presence of biliary disease, particularly when there is associated jaundice, hepatic and renal damage already exists and cannot fail to be intensified by the trauma of the anesthetic.

Ether, chloroform, nitrogen monoxide, gas and oxygen and in later years cyclopropane and ethylene have been used; in many cases the operations have been done with the use of spinal anesthesia either alone or fortified by one or more of the aforementioned drugs; in a few (Boyce and McFetridge) splanchnic anesthesia was used. The hepatorenal syndrome has apparently developed irrespective of the form of anesthesia or analgesia used or of the individual drug or combination of anesthetics employed. In a very few of my own cases anesthesia by local infiltration of the abdominal wall with 2 per cent procaine hydrochloride has been employed. In the experience of Walters and

Parham, the difference in reaction between general and local anesthesia has been a difference of degree only; if the urea content of the blood is taken as a criterion, it is established that in the cases in which disturbances occurred local anesthesia combined with administration of small quantities of ether was followed less frequently by disturbances of nitrogen metabolism.[2]

3. *Effect of Anoxemia; Anoxia.*—During experiments with general anesthesia and with eclamptic states, the idea suggested itself to Stander that one had to deal, perhaps, with varying degrees of asphyxia. According to Stander, anoxemia produces acidosis, as is evidenced by a lowering of the carbon dioxide–combining power, by hyperglycemia and by accumulation of lactic acid in the blood stream. It also produces marked degeneration and necrosis of cells in all parts of the lobule of the liver as well as slighter changes in the convoluted tubules of the kidney. These changes are not associated with the deposition of fat but appear to consist in simple necrosis of cells.

Hartman pointed out that when he compared his anatomic observations in the cases in which fever therapy was used and the patient died with those of Courville in his studies of asphyxia (or anoxia), he found a striking parallelism; he came to the conclusion that asphyxia must be one of the causative factors in the harmful effects of fever therapy. He found that after the production of high temperatures in animals severe asphyxia (anoxia) was shown by the decreased oxygen saturation of the arterial blood and the low oxygen content of the venous blood, and that when the saturation fell below 65 volumes per cent the animals died.

Moon has seen similar pathologic changes in animals and in human beings as a result of shocklike states produced artificially or occurring clinically. According to Hartman, the pathologic changes produced by high temperatures are similar to those of anoxia produced by prolonged asphyxia, by carbon monoxide poisoning and by acute alcoholism. The work of Hartman and Courville is in accord with such a conclusion, in that the pathologic changes are more pronounced the longer the patient lives after asphyxia has been established.

4. *Effect of Shock and Shocklike States.*—Shock (including the term collapse) is a generic term for a series of phenomena of similar nature which are found to be caused by, to follow or to be associated with a variety of preceding events. The symptoms of shock are well known. In all forms of shock one recognizes (1) an immediate form (primary shock) of varying degrees of intensity, frequently so severe as to cause death immediately or quickly, and (2) a delayed form (secon-

2. Compare this section with that on drugs and chemicals.

dary shock) which develops more leisurely in the first forty-eight to seventy-two hours after the appearance of the cause. This is a purely clinical differentiation.

Primary shock may be described as sudden great circulatory collapse, usually associated with loss of consciousness. It is often caused by a stunning blow or a serious disturbance of the central nervous system and may be likened to syncope or collapse. Secondary shock is characterized by low arterial blood pressure, by a rapid and thready pulse, by shallow, rapid or irregular respirations, by general restlessness and insatiable thirst, by coldness and often pulselessness of the extremities and by other evidences of circulatory disturbance. Unlike primary shock it is usually associated with a relatively clear mental state. It follows moderate or severe injuries, particularly those involving a good deal of muscular tissue and causing repeated small or severe hemorrhages.

The following forms of shock can be distinguished clinically:

A. Neurogenic Shock: Shock can be a psychic phenomenon, and as such, as far as present knowledge goes, it lies entirely outside the scope of this discussion. The sudden and frequently overpowering shock which follows a severe injury (physical, chemical or thermal) results from an overpowering stimulation of important nerve trunks, the spinal axis or the brain, and the mechanism undoubtedly varies from that of a simple or extraordinary reflex to that of a more or less complete paralysis of important nerve centers. Other factors commonly enter into the mechanism, especially the action of toxic bodies absorbed from injured tissue. The toxic effects of laked blood and of traumatized muscular tissue on the higher centers have been demonstrated in experimental animals.

B. Traumatic Shock: This includes shock produced by or following operation. It follows excessive trauma (traffic accidents or gunshot wounds) in which important or large areas of the body are affected to the point of pulpification or separation from the rest of the body and severe or prolonged operations (extensive intestinal procedures, important amputations of the limbs or radical amputations of the breast). The important element in traumatic shock is the absorption of toxic bodies from the injured and destroyed areas, and in this regard the mechanism seems related to that producing the effects of autolysis of tissue. As secondary contributing causes, neurogenic factors, hemorrhage and hemolysis enter into the mechanism of traumatic shock.

C. Shock Following Hemorrhage: All forms of shock are aggravated and intensified or caused by loss of blood. This is a mechanical phenomenon associated with the sudden marked diminution of the fluid content of the circulatory system and the tissues. When shock is due

entirely to hemorrhage, and the basic disturbance has not progressed too far, immediate relief is obtained by restoring the fluid content with dextrose and saline solutions, with acacia or, best of all, with whole blood. The mechanism is related to that of anhydremia and diminished volume of blood.

D. Hemolytic Shock: Hemolytic shock, which is dangerous, may follow blood transfusion if the blood groups of the donor and the recipient do not agree. Bogomolatz, Bajdasaroo, Vlados and others did not recognize hemolytic shock as a distinct entity but classified all complications following blood transfusion as colloidoclasia.

Hesse differentiated three forms of hemolytic shock. The first is acute, with mild vascular and cardiac phenomena which soon disappear. In this form about 50 cc. of hemolyzed blood can be taken care of by the reticuloendothelial system. The second is acute and severe, with a serious fall in the blood pressure. In 4 of Hesse's cases of this type death occurred within an hour and in 24 cases within a few hours. In some cases the chief sign was increased intestinal peristalsis. The third form of hemolytic shock described by Hesse is a delayed form, of which the first signs appear after periods varying from twelve to twenty-four hours. This form is infrequent.

The anatomic changes following hemolytic shock are most interesting: In Malijšev's patients and experimental animals there were the usual signs of hemolysis. In addition, when death was delayed for any length of time there were degeneration of the epithelium of the renal tubules and necrosis in the centers of the hepatic lobules. According to Malijšev, Skundina and Elanskij, such changes are not to be attributed to mechanical obstruction alone but rather to the anemic condition of the organs, the spasm of the capillaries and the toxic action of the products of decomposition of hemoglobin.

Hesse and his school subdivided the mechanism of hemolytic shock into four parts: (1) nonspecific protein reactions of varying intensity; (2) hemolytic shock and its sequelae; (3) intoxication of the organism by denatured proteins occurring in preserved blood, and (4) anaphylaxis.

Petroff and Iljin have shown that the toxic effect of heterogenous blood is related to its protein content. The introduction of either erythrocytes or plasma into the blood stream of experimental animals is followed by especially marked toxic effect and the toxic substances are similar to the complicated protein components of adenosin phosphoric acid.

E. Peritonitic Shock: Peritonitic shock, according to König, has a characteristic picture—a circulatory change, with dilatation of the capillaries and injury to their walls, which is followed by transudation. Holzbach added another factor by attributing the changes in the walls

of the vessels to toxic action. In the presence of peritonitis the blood gathers in the splanchnic area, particularly in the intestines and in the liver. In all forms of peritonitis infection is an important factor. In biliary peritonitis the toxic effect of extravasated bile is an added factor.

F. Shock Associated with Acute Intestinal Obstruction: The probable cause of the shock syndrome following intestinal obstruction is intoxication with histamine, with other products of injured and necrotic tissue and by absorption of bacteria and their products from the obstructed bowel.

G. Anaphylactic Shock: Occasionally, especially in experimental work, there are marked resemblances to the phenomena of anaphylaxis. In some cases the sensitization seems of major importance; in others anaphylaxis plays a minor role. In any case the anaphylactic manifestations seem always to be associated with the manifestations of other mechanisms.

H. Shock Produced by Action of Toxin: Nussbaum was the first to correlate the action of toxins with the production of shock. Experimental work has centered largely around shocklike states produced by trauma and hemorrhage. In animal experiments shock produced by traumatizing a limb does not appear until the tourniquet is removed from the limb; and during the World War an English research committee found that traumatic shock did not occur in the dog if the vessels of the extremity were clamped before the injury was inflicted. König showed that if injured muscle cells are macerated quickly enough, a substance is formed which in small doses is fatal to animals. Cannon, Sierra and Lemon and Schoercher suggested that this substance is histamine, and in experimental work histamine regularly produces a shocklike state. Similar toxins are elaborated from the platelets and from defibrinated blood. Zipf was able to demonstrate that these toxins are the nucleotides, especially adenylic acid and adenosin. Curiously enough, adenylic acid is found in the fluid secretion of the blebs caused by burns.

According to other investigators (Pannella), shock is an anaphylactic state caused by absorption of albuminous material from the destroyed tissues. It has also been pointed out that the toxic action of acetylcholine and carnosine (substances which are not foreign to the body) on the vascular system, in conjunction with the vascular dilatation resulting from neurogenic reflex action which causes irritation of the sympathetic and sensory nerves, would be entirely sufficient to explain the clinical phenomena of shock.

I. Shock Produced by Chemicals: In experimental work a number of chemicals and drugs have been used in the production of shocklike

states: these include germanin (König; Doelle), heparin (Keyes and Strauser; Doelle) and novirudin (sodium combined with humic acid) (Doelle). The experiments brought out the fact that the shocklike state does not occur when the blood is incoagulable; von Falkenhausen had shown this also for anaphylactic shock and Friedberger for peptone shock. The experiments showed that germanin, arsphenamine and heparin destroy the complement-forming and thrombotic properties of the blood. In this regard it is interesting to compare the clinical use of germanin in the treatment of pemphigus (see the section on the action of drugs and chemicals). The important point of all of this experimental work is that a shocklike state cannot be experimentally produced when the blood is incoagulable.

The process is seen in an exaggerated form in hemolytic shock after the transfusion of blood of an unlike group. Sudden hemolysis takes place as the result of liberation of the prothrombin (using up of the complement) from the antiprothrombin-prothrombin complex. Finally, Krehl concluded that the process is probably related to the endothelial cells, the liver or the bone marrow. König concluded that the liver plays a particular role as a depot organ and is the chief site of the formation of antithrombin (heparin). This is indicated by the enlargement of the liver, the central hepatic softening and the outpouring of glycogen in shock.

No one theory will explain all of the phenomena observed in shock. Many of the numerous factors involved—depression of the vital centers, anhydremia (loss of blood volume), dehydration, anoxemia (anoxia), acidosis and experimental factors in artificial shocklike states—have been reviewed in this communication, and the interrelations and similarities of the demonstrable anatomic lesions can be easily grasped from the factual presentation. It is evident that in many shocklike states typical changes have been demonstrated in the liver and kidneys. It is also evident that shock or a shocklike state is a complicated condition which can be produced by many agencies, including reflex or neurogenic action, trauma or disintegration of tissue. So many are the associated factors and so intimate are the associations of these with each other and with their provocative causes that it is difficult to say to which ultimate radical the hepatorenal symptoms and/or lesions should be ascribed.

5. *Effect of Dehydration and Anhydremia.*—Generally speaking, the daily normal loss of water, according to Maddock and Coller, includes from 800 to 3,000 cc. as urine, approximately 200 cc. in the stool and an insensible loss (by cutaneous evaporation) of from 1,000 to 1,500 cc. The maintenance of the electrolyte balance requires a daily supply of

approximately 5 to 6 Gm. of sodium chloride. In normal health the variations in these approximate figures are slight.

In abnormal conditions, even those of most transitory nature, the loss of water is increased because of vomiting, diarrhea and excessive sweating and because of ingestion of substances which normally increase, through their diuretic effect, the secretion of urine. In long-standing illnesses the amount of water lost per diem is increased, and the increase depends on the nature of the illness, on the presence of fever and on the importance of diarrhea and/or vomiting.

Various degrees of dehydration occur under the following clinical conditions:

A. In pediatric practice the effect of loss of fluid from the body in the first few days of extrauterine life is well recognized. High grades of fever are common, and it is well known that the lost fluid must be immediately replaced if untoward results are to be avoided.

B. In surgical practice, during operations of any magnitude, the loss of fluid, according to Maddock and Coller, amounts to approximately 1,000 cc. The loss of blood also may be considerable. The importance of replacing this lost fluid in order to alleviate the symptoms in the immediate postoperative interval or to avoid any further consequences is so well known that the practice of introducing fluid into the body has become a routine in almost every well regulated hospital.

C. As has been indicated elsewhere in this communication, similar losses of fluid, amounting under experimental conditions to between 20 and 30 per cent of the blood volume of the body, are known to occur as a concomitant phenomenon of the autolysis of tissue and after destruction of portions of the body by heat.

D. Similarly, loss of fluid occurs with local and diffuse forms of peritonitis and with intestinal obstruction.

E. Finally, the effect of loss of fluid on persons lost in the desert without water is well known. Death is the inevitable result. Unfortunately, I have no data and do not know where to find any concerning the pathologic effects, either morphologic or functional, on the human body of such conditions.

Accompanying any extraordinary loss of fluid there is an increase in the concentration of the blood, as shown by an increase in the percentage of hemoglobin and in the hematocrit readings. According to Mason and Lemon, the increased concentration of blood is due to a decreased volume of plasma, a decreased volume of serum and an increased fibrin content. The concentration of the blood, as shown by the increase in the percentage of hemoglobin and in the hematocrit reading, is according to Harkins roughly proportionate to the loss of

fluid, but the blood pressure remains near normal until death approaches and then falls rapidly.

According to Stander, peptone, histamine and histamine-free albumose each produce a blood picture suggesting anhydremia. The moisture content of the blood is lowered, although the increased concentration of the blood is perhaps not wholly due to this dehydration. It may be due also to actual loss of plasma, resulting from capillary dilatation.

Mason and Lemon proposed the hypothesis that any such extraordinary loss of fluid is productive of a form of secondary shock. They have also introduced the conception that the anatomic changes associated with the hepatorenal syndrome are due to the anhydremic condition which follows. Many other factors are all too often associated with the primary illness or with the operation which commonly is done. It seems difficult to correlate the anatomic changes with this one factor alone, although, as has been pointed out, it is constantly present and must be reckoned with.

6. *Effect of Autolysis of Tissue.*—Many facts of importance in relation to the hepatorenal syndrome and/or lesions are to be learned from a study of the facts and phenomena preceding and accompanying autolysis of tissue during life. Clinically this association is found under the following circumstances:

A. In cases of strangulation ileus: The effect of obstruction of the bowel has been considered. The studies of Wangensteen and Waldron showed that the autolysis of tissue accompanying strangulation ileus intensifies the effects of simple obstruction of the bowel.

B. In cases of traumatic destruction of tissues during severe injuries: This occurs with the tissues of the viscera as well as with the tissues of the superficial muscles. The incidence and other aspects of this condition as related to the liver have been discussed in a previous part of this communication.

C. In cases of necrosis of tissue occurring as an untoward and unexpected accident after surgical operations: The best example of this takes place in the liver, in which, very rarely, during operation on the gallbladder and bile ducts the main stem or an important primary branch of the hepatic artery is injured; necrosis of the appropriate segment of hepatic tissue follows. This is another variety of the condition described in the foregoing section.

D. In cases of burns: This subject has been extensively discussed elsewhere in this communication.

E. In gangrenous inflammations of the appendix and the gallbladder: Such inflammations also involve autolysis of tissue to some extent.

F. In cases of necrosis of tissue resulting from the application of radium: Many years ago I observed the following case in consultation:

> The patient was a middle-aged woman in excellent condition except for carcinoma of the fundus of the uterus. An intrauterine application of radium was given by the attending physician. Within a week the woman went into toxemia of the highest grade, with extreme hyperpyrexia; slight jaundice was present. Death occurred several days later. Postmortem examination showed peritonitis, total necrosis of the uterus and degenerative changes in the liver and kidney.

G. In cases of necrosis of large bulky tumors, such as uterine fibromyoma.

H. In experimental work: A great deal of work has been done on the phenomena which follow autolysis of tissue, by Mason, Davidson, Matthew and Rastello, Wangensteen and Waldron, Haden and Orr, Ellis and Dragstedt, Delbet and Karajonopoulos, Mason and Lemon, Andrews and Hrdina, Mason and Nau and others. Usually the experiments consist of placing within the peritoneal cavity pieces of the various abdominal organs, taken from the same or another animal and separated and disconnected from all of their biologic attachments. Mann noted similar effects when, in an attempt to remove the entire liver, pieces of unattached hepatic tissue were allowed to remain within the peritoneal cavity. According to Andrews and Hrdina, similar effects are noted when the pieces of tissue are placed within the pleural cavity or beneath the skin. In almost all the experiments the animals die within from one to two days.

The studies of Wangensteen and Waldron showed that pieces of the pancreas, the liver and the intestine are the most toxic; renal tissue is relatively nontoxic, and splenic tissue is intermediate in toxicity. Intestinal, pancreatic and hepatic tissue appear to disintegrate into toxic bodies more quickly than do renal and splenic tissue. The size of the autolyzing piece of tissue is also important, as Boyce and McFetridge pointed out. The injected substances prepared from the various tissues (Andrews and Hrdina) appear to be about equally toxic, except that there seems to be an early qualitative difference in the toxicity of the autolyzing tissues, in accordance with the rapidity of disintegration and liquefaction. With transplants of hepatic tissue Mason and Nau have noticed differences in accordance with the point from which the transplants are taken.

The pathologic pictures encountered by Mason and his associates, by Wangensteen and Waldron, by Boyce and McFetridge, by Andrews and Hrdina and by others, in experimental animals presented strong similarities. The animals were found dead in from ten to eighteen hours. In such experiments the abdomen is generally distended with gas if

the animal lives more than twelve hours; between 300 and 500 cc. of blood-stained exudate is present within the peritoneal cavity, and gas is present in the exudate and on the surface of the liver and of the other viscera. Generally deposits of fibrin and of frank pus are comparatively rare. The entire peritoneal surface is intensely inflamed and hemorrhagic. The hemorrhages occur also in the other endothelial surfaces of the body, especially the pleura, and in the lung.

The most striking changes occur in the host's liver. It is infiltrated with gas, and far advanced degeneration and necrosis are scattered throughout. There is minimal infiltration with leukocytes.

Turley's description of the microscopic pictures in the liver and kidney, as given by Mason and Nau, is as follows:

> Cords of central and middle zones of the lobules [of the liver] show rarefaction so marked that the nuclei of the cells appear to be held in place by a lace-like web. The cells of the peripheral zones have a fine, foamy appearance. The tissues of the portal canals are infiltrated with lymphocytes, endothelial cells, and an occasional polymorphonuclear leucocyte. This infiltration is most marked around the bile ducts. The liver is the victim of what appears to be a rather acute and marked fatty degeneration plus a septic cholangeitis.
>
> The lesions in the kidney vary with the different fields. In some fields the capillaries of the tufts and tubules are engorged with red blood cells, the tufts are swollen until they fill the subcapsular spaces, the tubule epithelium is swollen, and the inner margins are frayed. The lumen contains granular débris. In other fields the glomerular tufts are approximately normal in size, leaving a fair subcapsular space. The tubular epithelium shows some erosion, but also many of the cells show the brush-like inner border. This kidney appears to be recovering from a rather intense, toxic parenchymatous nephritis. The cause of the condition is still operating though in lessened intensity as is shown by the areas of present, acute nephritis.

Andrews and Hrdina emphasized the fact that

> It was almost impossible to distinguish between the appearance of the transplanted liver and the host's liver. Both showed almost equally severe autolytic changes. On microscopic examination, while the transplanted liver showed more advanced necrosis, the host's liver showed such changes that one could not be sure without reading the labels on the slides which was which.

Boyce and McFetridge have criticized the interpretation of the microscopic pictures stressed by Andrews and Hrdina, on the ground that they have seen such pictures only when postmortem examination was delayed. It is true that production of gas continues after death, and the greasy appearance or feel of the liver might be a postmortem effect. Nevertheless, it is difficult to associate infiltration by lymphocytes, leukocytes and endothelial cells and the appearance usually associated with cholangitis with anything except biologic changes, which can occur only during life.

A minority of observers (Dragstedt) have not been convinced that toxemia can result from autolysis in the absence of bacterial growth; they have concluded that the dominating factor is the growth of bacteria in the liquefying tissue.

The bulk of the experimental evidence, however, shows that death which occurs under conditions of autolysis is not produced primarily by infection; the customary presence of the gas-producing Welch bacillus indicates a concomitant, contributory, catalyst-like and synergistically intensifying factor in the fatal outcome. Rather does it seem that death is primarily due to a toxemia of maximum grade. The evidence shows that the toxin is produced in the process of autolysis of the implanted tissue in the experimental animal or the destroyed and/or necrotic tissue in the human being. According to Andrews and Hrdina, the toxic agent is a water-soluble thermostable body which is precipitable by alcohol or chloroform, stains purple in solution when the biuret test is used, is with difficulty dialyzable and probably falls within the albumose group. In support of this opinion, Andrews and his co-workers have cited the fact that the anaerobic bacilli recoverable from experimental animals after death are not toxic when injected intraperitoneally or intravenously. Boyce and McFetridge expressed agreement with this opinion.

7. *Effect of Acute Peritonitis.*—Acute peritonitis occurs as a complication of many of the conditions described in this communication—trauma, infections and all types of abdominal operations. The role of peritonitis is, then, commonly secondary. Whatever symptoms are present in the liver and kidney should be referred to the primary condition when peritonitis is secondary or metastatic. In addition, in this form as well as when the peritonitis is primary and results from trauma, associated factors (neurogenic factors, shock, collapse, dehydration and toxemia) develop; the role and importance of the latter in the pathogenesis of hepatorenal lesions and/or symptoms have been previously outlined in this communication.

Biliary peritonitis has been observed by Touroff in a small series of cases in which the hepatorenal syndrome was present, and he has suggested that the biliary peritonitis is the cause of the syndrome. This has not been corroborated in other clinics. In addition, as can be seen from the factual presentation in this communication, there are many other factors to consider, and biliary peritonitis cannot be considered a possible cause in many of the cases recorded in the literature.

In all cases of peritonitis the factor of infection dominates the picture, and in spite of many associated conditions, whatever hepatic and/or renal changes occur are probably directly due to this factor more than to any other.

IV. EXPERIMENTAL PRODUCTION OF LESIONS IN THE LIVER AND KIDNEYS

Experimental investigations have attempted to produce in animals hepatorenal lesions acceptably similar to those observed in human beings, but have not generally succeeded. In general, the investigations have followed the following trends:

1. *Traumatic Destruction of Parts of the Liver.*—Helwig and Schutz and Boyce and McFetridge have worked along these lines. The results have not been altogether satisfactory. Nevertheless, the clinical experiences previously referred to in this communication regarding clinically observed pulpification of the liver cannot be dismissed. Some of the experiments in autolysis of liver and of tissue lend considerable weight to these investigations.

2. *Interference with Hepatic and Portal Circulation.*—Investigations of this nature have been made and reported by Ravdin, Behrend, Boyce, Lampert and McFetridge, Helwig and Schutz, Helwig, Schutz and Kuhn and others. These experiments have given no positive evidence regarding hepatorenal lesions. In one experiment made by Gundermann, however, uremia followed ligation of the hepatic artery. In other experiments Gundermann tied the left portal vein; atrophy of two thirds of the liver developed; oliguria followed, with albuminuria, and casts and red blood cells appeared in the urine. The latter experiment probably had more relation to the experimental production of cirrhotic conditions of the liver.

3. *Obstruction of the Biliary Tree.*—This procedure has been successful in reproducing hepatorenal lesions in animals, especially when the obstruction was later suddenly removed. Most of this work was done by Boyce and McFetridge.

4. *Injection of Extracts of Damaged Liver.*—Attempts have been made to reproduce hepatorenal lesions by the injection of extracts of the livers of animals in which hepatic damage had previously been produced by:

A. Obstruction of the biliary tract, with and without subsequent sudden release of the obstruction.

B. Injection of various chemicals.

C. Disease and/or operation (as in a case of "liver death").

The experiments were made by Boyce and McFetridge, who obtained positive results only with the extract from the animal who had suffered "liver death." They pointed out that only saline solution or watery extracts give positive results and explained the failures on the basis of that fact, and of the probable insufficiency of dose or concentration of the causative agents in other experiments.

5. *Implantation or Injection of Normal Liver and/or an Extract of Normal Liver.*—This was done in the course of experiments on autolysis of tissue by Mason and associates, Dragstedt and his co-workers, Andrews and Hrdina and Boyce and McFetridge. The experiments failed to produce either a clinical picture or lesions which in the opinion of the experimenters were similar to those observed clinically.

In contradistinction to these experimental results, Pytel stated that he was able to reproduce the hepatorenal syndrome in rabbits by ligation of the hepatic artery, by subcapsular traumatization of the liver, by intraperitoneal and intravenous injection of extracts from the livers of animals in which the syndrome was produced and by injection of blood from such animals into normal animals.

COMMENT

PHYSIOLOGIC, COMPLEMENTARY AND CLINICAL ASSOCIATIONS OF LIVER AND KIDNEY

The close association of the liver and the kidney in the performance of certain metabolic processes dealing with detoxification of various substances by the former and their excretion by the latter suggests definite interdependence.

The literature dealing with more obscure relations between the kidneys and the liver has been fully reviewed by Lieber and Stewart, Henschen and Rosenbaum, and other recent investigators (Mayer, Sacchetto and Oselladore, Bompiani and Koch) have pointed out the association of certain individual lesions occurring in these organs. According to Stäheli, Dourmashkin and Fitz-Hugh, operative manipulation of the extraparenchymatous conducting system of either the liver or the kidney may result in reflex suppression of the functional activity of the other organ. In addition, clinical (Porges and Grossman) and experimental (Asher, Meier and Mosonyi and Voith) observations, including the results of administration of liver extracts to animals (Lampe, Glaubach and Molitor) suggest that the regulatory mechanism of renal function originates in the liver. Similar evidence is supplied by the work of Gundermann; Haberer; Narath; Mann; Dicker and Andersen; Allan, Bowie, McLeod and Robinson, and Whipple and Speed.

Pytel called attention to the complementary nature of lesions of the liver and the kidneys. In most of the reported cases a secondary renal effect or impairment developed after primary disease or traumatic impairment of the liver; in a lesser number a primary renal lesion was followed by hepatic manifestations.

Dourmashkin's report, made in 1928, described 2 cases of coexisting urethral stricture and hepatic cirrhosis. A few hours after sounding of the urethra of the patients a chill and high fever occurred; drowsiness followed; recurrence of

previously existing jaundice was then noticed and deepened rapidly; a typical cholemic picture finally developed, and the patient died. The course of the second patient was similar.

Dourmashkin's report undoubtedly stimulated the report of Fitz-Hugh along similar lines. The latter author described typical hepatorenal syndrome with liver-to-kidney progression in 1 of his cases, while the next case reported by him was one of primary urologic disease, in which instrumentation was followed by chills, fever and other urologic symptoms indicative of infection and one week later by jaundice and other clinical and laboratory evidences of hepatic involvement.

There is no doubt that the mechanism of transfer in such cases operates through infection; nevertheless, the complementary effect is well illustrated in these reports. In Dourmashkin's cases no drug was used which could possibly, in urologic involvement, have produced the hepatic symptoms and lesions and the terminal cholemia. In Fitz-Hugh's cases some form of local anesthesia was employed, and all of the patients had a background of previous use of drugs (alcohol, arsphenamine and other substances) which might have predisposed to hepatic damage. In Pytel's opinion these observations indicate a strong functional hepatorenal relation.

PHYLOGENETIC RELATIONS OF LIVER AND KIDNEY

According to Lieber and Stewart,

The existence of a phylogenetic relationship has been demonstrated in fishes, amphibians, reptiles and other lower vertebrates and, according to Roger and Spanner, in birds in which both the liver and the kidneys possess afferent portal veins. In mammals the kidneys have a portal venous supply in early embryonic life (Spanner), and although this tends to undergo involution there are indications that vestiges of it may persist and become functionally active in adults under certain conditions. Hemorrhages in the renal cortex, regressive changes in the epithelium of the renal tubules and the development of large, finger-like anastomoses between branches of the renal and portal veins have been encountered both in animals (Claude Bernard, Villaret, Tuffier and Léjars and Villaret and Justin-Bezancon) and in human beings with increased portal pressure (Léjars, Giacomini, Henle, Virchow and Hyrtl). According to Rosenbaum, this vascular mechanism may be responsible in part for the occurrence of renal changes following extensive damage to the liver, some of the blood from the portal vein being carried directly to the kidney by way of the ordinarily unused collateral blood channels.

There is no doubt that some of the vagaries of the quantitative or qualitative distribution of hepatic and renal lesions are at least partially accounted for by the existence of the separate vascular circulations through the liver and kidneys. It is possible and probable that at certain times and from certain areas (for instance, the mesenteric area) material is always passed primarily through the liver, whereas at other times and from other areas (for instance, the general circulation, as in chemical poisoning, or the lower portion of the intestine), material is passed directly into the vena cava and, without the intervention of the

liver, directly through the kidneys. Under the latter circumstances hepatic lesions and manifestations may be at a minimum or entirely absent, and the renal lesions and phenomena may be dominant and at a maximum.

DISTRIBUTION OF SIMILAR DEGENERATIVE LESIONS IN OTHER PARENCHYMATOUS ORGANS

In addition to the anatomic, functional and phylogenetic relations between the liver and the kidneys, the association of symptoms and/or lesions of the liver and kidneys is further complicated because of the fact that in postmortem protocols similar degenerative changes are sometimes noted as having occurred in the brain, the adrenal glands and other parenchymatous organs (Wilson; Bardeen; Weiskotten). Postmortem changes are also well known, and their mere mention should indicate the necessity for, and the occasional difficulty of, their proper integration.

GENERAL SIMILARITY OF LESIONS

On the basis of the observations made in the present study, no sharp differentiation can be made between the lesions occurring in association with primary pathologic conditions of the liver and biliary tract and those found in association with any of the other diverse conditions described. Although the former may appear to be somewhat more marked, the apparent preponderance may be discounted to some extent because, first, the hepatorenal syndrome does not develop sometimes when one has every reason to expect it; and second, the extreme variability of human pathologic material and the difficulty of evaluating the influence of variable and uncontrollable factors render it impossible to attribute much importance to such quantitative or even qualitative differences.

OCCURRENCE OF HEPATIC AND/OR RENAL LESIONS CLINICALLY

It must be emphasized that the hepatorenal syndrome does not always develop under the same conditions. It is sometimes difficult also to reconcile any particular manifestation or factor with the general mechanism and pathologic picture involved in the biologic concept. All this is baffling. A number of explanations, however, appear:

1. There is no doubt that in this, as well as in other medical matters, the appearance or nonappearance of the symptoms and/or lesions bears an important relation to the severity of the primary cause, to dosage if the condition is caused by a drug, or to the extent and severity of the preceding state. A good example exists in the manifestation of jaundice. For instance, it is difficult to explain, except on a quantitative basis, the presence or absence of jaundice in cases in which the hepato-

renal syndrome is traumatically produced. It may depend on the amount of hepatic tissue destroyed. On the other hand, the jaundice may be brought about purely mechanically, by obstruction of a sufficient number of the larger ducts by pulpified hepatic tissue, by secondary swelling of the tissues surrounding the duct walls and of the duct walls themselves or by both of these mechanisms. This seemed to be an important element in Helwig and Orr's case, the report of which said that "the pulpified liver tissue . . . was so located as to include the larger proximal ramifications of the right and left hepatic ducts." A possible aid in arriving at the mechanism of the jaundice in Helwig and Orr's case, which might be furnished by study of the qualitative variations of the van den Bergh test, is not available in the protocol furnished by these observers.

2. An important suggestion, made by Rabinowitz, that sensitization of the liver to protein (whether by surgical trauma, inhalation, ingestion or parenteral injection), opportunity for which is sufficiently abundant in everyday life, renders the liver increasingly susceptible to the toxic damage may help to explain the reason why some patients go through a rather fulminating course to death while others show mild symptoms and eventually recover or possibly show no symptoms at all. The sensitization which occurs after repeated burns has been mentioned specifically by Duval.

3. There is no doubt that in many cases more than one factor is operative in producing the hepatorenal disturbance. The resultant action is cumulative or synergistic in the cases in which the hepatorenal syndrome appears and is sufficiently powerful to cause the symptoms or lesions in the liver and/or the kidney.

4. The amount of compensatory effort in any parenchymatous organ is, as is well known, large; and nowhere is this effort greater than in the liver and kidney. It cannot be otherwise than that this factor of safety plays an important part in determining the manifestations of disease in these two organs. This also bears an important relation to the powers of resistance of any person.

NONSPECIFICITY OF HEPATORENAL LESIONS AND/OR SYMPTOMS

In contradistinction to the opinions of Helwig, Schutz, Kuhn and Orr and Boyce and McFetridge, none of the observed facts will permit one to assume any specificity of mechanism or pathogenesis in the production of the hepatorenal lesions. Abundant experience has shown that hepatic necrosis occurs under a variety of clinical conditions. Even the complicating states and factors previously discussed in this communication are found in a variety of other clinical conditions, and

there is no convincing proof that they are specifically bound to the hepatorenal lesions.

It is not correct to ascribe any specific nature or character to any hepatic cell toxin or to its action on the kidney. Any toxin developed in the hepatic cell because of its degeneration is biologically a tissue toxin, which, surely, is similar to the tissue toxins developed in the course of degeneration of other cells, such as occurs, for instance, after burns of the skin or traumatic destruction of muscles. Finally, many renal manifestations occur also under circumstances far removed from those under discussion.

SIMILARITY OF EFFECT PRODUCED BY A VARIETY OF CAUSES

In any consideration of the causative factors associated with the hepatorenal syndrome it should be noted that a similar effect may be produced by a variety of causes. Good examples are afforded by superficial burns, traumatic destruction of the superficial musculature and autolytic necrosis of parenchymatous organs. In each of these, destruction of cells and undoubted changes in intercellular tissues occur because of the application of heat, because of the physical destruction of normal relations and structure and because of chemical (and/or bacterial) action. Profound and excessive neural stimulation and hemorrhage are present in two and local loss of fluid in all three. The end result is, nevertheless, the same whatever the cause and encompasses a change in chemical and morphologic structure and the production of a state clinically recognized as shock.

ASSOCIATED GENERAL CONSTITUTIONAL OR OTHER FACTORS COMPLICATING HEPATORENAL LESIONS

Many patients whose illnesses are of interest in the present discussion were above the age of 40, and many of them, in addition, were afflicted with certain conditions—undernutrition, obesity, diabetes, hypertension, cardiac disease or nephritis—which commonly appear when a person passes 40. Postmortem protocols on such persons commonly lay bare various degenerative lesions—fatty degeneration, vacuolar degeneration or pressure necrosis in passive venous congestion—which physicians have come to associate pathogenetically with age, with the normal wear and tear of tissue, with the effects of the aforementioned abnormal states and possibly with other obscure factors.

HYPERACUTE, HYPERPYREXIC FORM—SO-CALLED LIVER DEATH

It has been said that the manifestations in cases of hyperpyrexia death (so-called liver death) are more or less similar to those in cases of delayed hepatorenal syndrome, and to a certain extent this is true.

Many clinical symptom complexes, however, have such general similarities. It has repeatedly been claimed that the differences in the character and extent of the pathologic lesions demonstrable in these two groups are only quantitative and depend on the length of time the patient lives after the inception of the biologic process. The latter statement, it seems to me, begs the question to a certain extent, as there is no completely indubitable evidence that the time element is so important. In certain cases of either type no lesion of any kind is demonstrable. Nevertheless there is no doubt that it must take some time for any lesion to reach its maturity or, at least, its demonstrability.

As a matter of fact, the preceding factual résumé seems to indicate that the outstanding manifestation, namely, the hyperpyrexia, is itself capable of producing the hepatic lesions. It would be logical, therefore, to hold that the pathogenesis of the condition leading to hyperpyrexia death is independent of the hepatic lesion and that the entire manifestation and the usual fatality are due to something else. Up to the present time no conclusive evidence has refuted this opinion. There are other medical and surgical situations, notably the crises in cases of thyrotoxicosis, in which a similar symptom complex follows disease and operation and in which hepatic changes and lesions are known to be secondary to the thyroid disturbances, which bolster up this point of view strongly.

There is no doubt that the dramatic intensity and fulminant development of the symptoms in cases of hyperpyrexia could be due to an overwhelming bacterial infection, as witness conditions occurring after any number of other types of operation in parts of the body widely removed from the liver and under widely different circumstances, in which it is known that the similar clinical course is due to infection and to infection alone.

In any case the impetuousness of the hyperacute form is related to the size of the dose of the causative agent; to the presence or absence of any associated allergic mechanism; to the symbiotic action of any mixed bacterial infection; to the synergistic action of associated causes and to the suddenness of the force which produces or sets in motion the pathologic changes. The abruptness of action necessarily produces an overpowering effect and becomes a compelling agency in the generation of functional and anatomic changes. There is no opportunity for adequate preparation and counteraction, as there is in cases in which the compelling factors develop slowly. This factor has special force in the cases of rapid death with hyperpyrexia, as well as special application in those in which the condition develops when any obstruction is released suddenly.

Many mechanisms have been involved in the sudden production of overpowering symptoms when an obstruction is suddenly released. The compelling agency has been correlated by various observers with various

states, such as anesthesia, shock, infection, absorption of toxins, dehydration and alkalosis. While the question is still not completely settled, present knowledge inclines one to the opinion that the production of symptoms is related to destruction of tissue at the site of obstruction (ulceration, gangrene) and to the greater facility thus produced for the flooding of the organism with tissue or with bacterial or possibly other obscure toxins. Possibly the newer knowledge of allergic mechanisms and hormonal action may add light to the problem, and continued investigation may bring forth neurogenic factors which may help to explain the acceleration and intensification of the pathologic mechanisms and effects.

In some of the reported cases in which hepatorenal lesions and/or symptoms appeared (compare especially the section on the effects of fever therapy) similar degenerative lesions were found in other organs, for instance, in the brain. Should such degenerative lesions affect the centers controlling body temperature, it is not inconceivable that the hyperpyrexia encountered clinically might be a direct result of such localization.

The explanation of the mechanism of liver death cannot be lightly dismissed as a "liver effect." Too little in general is known to justify trying to explain the phenomenon of death on any such basis. It is true that in the sense that hepatic function is intimately bound up with the phenomena of life its cessation is just as intimately one of the phenomena of death. All this, however, is philosophy and not medicine.

RELATION OF THE HYPERACUTE HYPERPYREXIC FORM (SO-CALLED LIVER DEATH) TO THE DELAYED CLINICAL AND PATHOLOGIC MANIFESTATIONS IN THE SO-CALLED HEPATORENAL SYNDROME

There seem to be two types of hyperpyrexia death. In one the clinical manifestations and hyperpyrexia are demonstrably unaccompanied by anatomic changes in the liver and kidney. Clinically, the picture is that of hyperacute infection, and it seems to me that it should be excluded from the general category of hepatorenal syndrome. In disease of the biliary tract following operation the manifestations of hyperacute infection have not, in my own experience and in that of many other clinical observers, been accompanied with the characteristic hepatic and renal changes, have commonly been associated with other competent causes of the symptoms and pathologic conditions and have impressed me strongly as evidence of overwhelming bacterial infection. I believe that this type should be classed not with the hepatorenal syndrome but rather with the broad group of bacterial infection.

In the second group, with similar clinical manifestations and hyperpyrexia, anatomic lesions can be demonstrated in the liver and kidney.

These anatomic changes have been most marked when the condition was caused by trauma, and it seems to me that only such suddenly produced conditions can show any resemblance to the symptomatic and anatomic manifestations of the delayed hepatorenal syndrome. One can understand that in the case of trauma the development of the symptoms and lesions would be rapid, owing to the character of the inciting cause.

HEPATIC LESIONS

It must seem obvious from all of the preceding facts, from the domination of the liver and the protean character of its functions and biologic connections with digestion and metabolism that more than one cause or set of causes may initiate a mechanism which would produce the characteristic degeneration of hepatic cells. In clinical practice a breakdown can occur in persons whose hepatic structure and function had previously been apparently normal, or, perhaps more probably, in persons in whom some hepatic damage had already existed. From the factual knowledge and experience previously reviewed in this communication it must be concluded that: 1. The number of apparent and/or apparently unrelated potential causes must be large and must include the following: chemical bodies, introduced from without the body or produced within the body as a normal or abnormal metabolic event and (in either case) either neutralized or not promptly excreted; bacterial infections, and tissue toxins of various origin and probably related chemical structure, produced by destroyed or degenerating tissue (as after trauma or burns). 2. It is probable that in the vast majority of cases some obscure combination of bacterial and chemical toxin is the essential provocative cause. 3. Therefore, this combination of causes can be equally operative in cases of primary hepatic disease, of thyrotoxicosis, of burns, of other primary or secondary conditions enumerated in this review, or possibly, of still other as yet unidentified and obscure conditions.

In various conditions the localization of the cellular degeneration in the hepatic lobule has varied from the center of the lobule to its periphery. This may be an accidental distribution of the action of the causative toxic body; it may depend on other circulatory changes, or it may be of no biologic importance. The essential fact is that degeneration of hepatic cells occurs in many clinical conditions and can be reproduced, under certain conditions, in some experiments on animals.

RELATION OF THE HEPATORENAL SYNDROME TO DISEASE OF THE LIVER AND THE BILIARY TRACT AND THE CAUSE OF ITS INCEPTION

In many cases of disease of the liver and biliary tract the bulk of the evidence seems to show that some form of hepatic damage has preceded

the onset of the illness and that it eludes diagnosis. In some cases the hepatic disability is demonstrated on the operating table as a gross change in connective tissue (cirrhosis) or as an interference with the portal circulation because of the presence of some degree of ascites. The presence of associated enlargement of the spleen indicates that some form of toxemia is present. The degree of hepatic damage thus shown varies a good deal, while in general the anatomic changes are more or less proportional to the amount of hepatic damage. The amount of reserve which is left, from which one may attempt to determine the prognosis, is not usually apparent, demonstrable or measureable.

A much greater degree of invisible pathologic change exists when jaundice appears. The change is always physicochemical and indicates severe changes and a state of emergency. When superimposed on any of the demonstrable changes mentioned in the preceding paragraph, it indicates a long-standing, perhaps usually an irreversible, pathologic condition. In many cases it indicates a terminal stage of the illness, and in any case a lack of hepatic reserve approaching the absolute. Commonly such a condition is associated with renal manifestations.

When the signs of the hepatorenal syndrome appear in such cases, one must assume that they represent a continuation of the preceding functional and anatomic pathologic process. In the absence of operative intervention the development of the picture is rather slow, although usually, as complete dissolution approaches, an apparent hastening of the process and a more rapid development seem to take place. When the alarming symptoms appear after an operation, it is probable that a measure of bacterial infection has been introduced, which, superimposed on whatever else has preceded, becomes "the straw which breaks the camel's back."

With acute or chronic cholecystitis and cholelithiasis, there is no doubt that some, at least, of the patients who reach the operating table have no such hepatic disturbance. Again, the bulk of the evidence seems to show that the hepatic or hepatorenal symptoms and lesions are then due primarily to bacterial infection and secondarily to later appearing, complicating conditions; the latter have all been previously indicated.

In cases of trauma producing pulpification of hepatic tissue a combination of causes seems to be operative. This may include the development of a tissue toxin, the secondary introduction of bacterial infection and the changes which accompany the appearance of any form of jaundice.

Whatever disturbance occurs is intensely magnified if jaundice is present. The abnormality depends on either or both of two factors: (1) the presence of obstruction of the major duct and (2) the state of the liver cell filter, which either is competent, in which case no

jaundice occurs, or is incompetent or interfered with, when jaundice follows. It seems to me that in cases in which trauma is present the appearance of hemolytic jaundice is of little practical importance because of the amount of blood extravasated and reabsorbed and because of other demonstrable factors.

VALUE OF TESTS OF HEPATIC FUNCTION AND/OR DAMAGE

The many chemical and biologic tests which have been proposed for the study of hepatic damage are bound up with tests of hepatic function. Dye excretion tests of many sorts and chemical tests based on metabolic change have been tried out and found disappointing. In most cases hepatic function is demonstrably maintained by compensatory effort, as bile is still present in the stool, since there is no impairment in glycogenesis or any evidence of failure to deamidize the amino acids, in that urea formation is unhampered and a progressive increase of nitrogenous products in the blood is observed. The clinical picture of well established disease, marked by abdominal distention, vomiting, rise in temperature, oliguria, appearance of albumin, casts and red cells in the urine, increase of residual nitrogen in the blood bleeding into the mucous surfaces and blood in the vomitus and the stool, indicates only too well the severity of the illness and the fact that coma and death are approaching. For that reason it is imperative to know the manifestations, which I pointed out some years ago, that indicate that such a severe and perhaps fatal condition is approaching. These are as follows:

1. Severe general symptoms, especially fever and chills. This item is possibly of least importance.

2. Anorexia or vomiting beyond the temporary or mild forms observable in the early stages of extrahepatic lesions of the biliary tract.

3. Shrinkage of the liver. This does not include the shrinkage of a temporarily swollen liver back to normal size. When this evidence is reliable and indicates a decrease below normal, it becomes the most important single clinical indication of destruction of hepatic cells and impending hepatic toxemia. The ultimate stage of such shrinkage is that known ordinarily as acute yellow atrophy.

4. Increasing jaundice.

5. Any tendency to hemorrhage.

6. Diminution of the secretion of urine, not accounted for by a corresponding diminution in the intake of fluid and with or without laboratory evidence of diminished renal function.

7. Demonstration of leucine or tyrosine in the urine.

8. Retention of nitrogen in the blood.

9. Signs of disturbed cerebral function—convulsions, stupor and coma. These are evidences of impending or established hepatic ("cholemia") or of hepatorenal ("uremia") intoxication.

In cases in which operation has been performed additional facts are available:

10. An operatively demonstrated cirrhotic condition of the liver. This indicates far advanced disease and one in which terminal manifestations may occur at any time. The presence of any degree of ascites only intensifies the significance of such findings.

11. Undue prolongation of postoperative vomiting for which no other competent cause is demonstrable.

12. Sudden and large diminution in the discharge of bile from an external biliary fistula, other facts and factors remaining equal and unchanged.

13. Marked diminution in the amount of bile in the stool in the absence of a discharging biliary sinus, other factors remaining equal.

14. Appearance of postoperative jaundice or any pronounced increase in previously existing jaundice.

It follows from all of these facts that the best and most competent idea of hepatic damage must still be based on more or less purely clinical grounds and that laboratory aid, while it may in some cases corroborate clinical impressions, is of little practical use. If a measure of the risk of any contemplated operation is to be attempted, or if, operation having been done, an opinion as to the prognosis is to be made, it must also be based on clinical observation, insight and experience, aided, to some extent, by laboratory data.

RENAL ELEMENT AND THE VALUE OF FUNCTIONAL TESTS

In 1911 Clairmont and von Haberer reported 5 cases of renal failure following operation on the biliary tract, in 3 of which fatality occurred. In the same year Steinthal noted anuria on the fourth day after operation on the common bile duct; autopsy showed acute tubular degeneration of the kidney. In 1911 von Beck and Simon witnessed death from uremia of patients on whom no operation had been performed. In 1921 Stäheli reported a case in which cholecystectomy and choledochostomy had been followed by death and referred to a similar case of Kehr. In 1922 Walters and Parham reported several instances of death from renal insufficiency after operation on the biliary tract. An extended report on the same subject was made by Wilensky and Colp in 1927. In 1933 Bartlett discussed and emphasized the renal factor in delayed death in the hepatorenal syndrome. Important experimental work was also done by Rowntree, Snell and Greene and by many others.

EFFECT OF THE EXCRETION OF BILE THROUGH THE KIDNEYS

The passage of bile and biliary components through the kidney, which occurs in cases of biliary obstruction, is usually, although not always, productive of renal abnormalities recognized clinically by the presence of albumin and casts in the urine. In cases of mild or early involvement an increase in the nitrogen content of the blood is not always demonstrable. This probably is the reason why the experimental work of Clairmont and von Haberer and that of Rowntree, Snell and Greene did not produce any retention of nitrogenous bodies in the blood, even though in their clinical observations Clairmont and von Haberer found evidence of renal failure in the jaundiced patient. Stäheli emphasized the importance of the duration of the hepatic disturbance.

The experience of the Mayo Clinic, as given by Walters and Parham, confirms the fact that in cases of severe involvement the influence of any hepatic disturbance on the renal mechanism is marked.

> Hepatic insufficiency . . . differs from renal insufficiency; associated with the former there is abundant drainage of light colored bile, containing small amounts of the bile pigments. Patients become restless, then drowsy and stuporous, and finally succumb. During the entire course of the hepatic insufficiency little change occurs in content or volume of the urine, and the blood urea remains persistently low. Renal insufficiency is associated with the cessation of the drainage of bile. But with the cessation of drainage, evidence is shown in the urine from day to day of a progressive nephritis. During this period of renal insufficiency secondary to the damming back of the bile in the circulation, the jaundice deepens, the coagulation time of the blood lengthens, and the blood urea progressively ascends to the level of uremia.

RELATION OF THE RENAL TO THE HEPATIC LESION

From the facts outlined in this communication, it seems that renal effects occur because of two preceding circumstances:

1. Certain functional and anatomic changes occur in the hepatic cell and its environment which produce profound changes in normal hepatic metabolism, in that normal products are prevented from being excreted and normally and customarily produced, or abnormally produced and unaccustomed toxic bodies are prevented from being detoxified or neutralized. The resultant clinical picture I have previously designated as "hepatic toxemia," a primary effect of the initial disease.

In many cases (though not in all) the kidney, which after the liver is the great excretory and detoxifying organ of the body, fails to take up the latter function of the liver when the liver breaks down, because the kidney is not normally fitted to handle many of the normal products of hepatic metabolism or the abnormal toxic bodies liberated in the damaged liver cell environment. The kidney promptly breaks down in

its turn and becomes an important and frequently a decisive factor in the total subsequent dissolution. This is the secondary effect (the third or last stage), which clinically I have previously designated as "renal toxemia."

2. When the preceding source of the entire disturbance is not in the liver proper, as indicated previously in this communication (for example, destruction of tissue in burns), or when the original cause is bacterial infection, and especially when the distribution of the causative changes occurs either partly or wholly by paths not traversing the portal area, renal symptoms can occur independent of any preceding hepatic symptoms. Under such circumstances any hepatic symptom which may be present is probably concomitant.

DISTURBANCE OF RENAL FUNCTION

In clinical practice functional disturbance in the kidneys is best measured by the degree and extent of any accompanying azotemia. Azotemia occurs in association with the following conditions:

1. Severe and protracted vomiting.
2. Immoderate and severe loss of intestinal contents either through the natural exit or through an artificially produced intestinal fistula, especially when it is present high up in the alimentary canal.
3. Diabetes with acidosis, especially in the stage of coma.
4. Hypofunction (Addison's disease) or experimental removal of the adrenal glands.
5. Traumatic shock.
6. Extensive burns.
7. Acute coronary thrombosis.
8. Profuse hemorrhage.
9. Diseases of the liver and biliary tract such as are under discussion in this communication.
10. Circulatory failure and collapse following operation, trauma or disease.

A considerable degree of azotemia may exist without any apparent effect on the symptoms or on the clinical picture. Usually, however, there are asthenia, vomiting, failure of appetite and disturbances of the sensorium. It is difficult to estimate the role of vomiting. Often it ushers in the disturbance; in other instances it occurs after azotemia is discovered; in many cases the one seems to accentuate the other, and a vicious circle is established.

The urine may be normal; commonly, however, the usual laboratory evidences of "nephritis" are present. Various degrees of oliguria are present; complete anuria, however, never occurs. Sometimes, especially

in the presence of extrahepatic symptoms, the opposite state exists, and normal or even abnormally large amounts of urine are secreted and voided. The concentration of the urine is variable. The disturbance is often reversible to normal after satisfactory intravenous administration of abundant fluids containing salt and sugar and sometimes of whole blood. Sooner or later pronounced peripheral circulatory failure occurs when death is to be expected, and an index of improvement in any such vascular condition is an increase in the peripheral blood pressure.

RENAL LESIONS IN THE PRESENCE OF DEMONSTRABLE AZOTEMIA

It seems to be a fact that a renal lesion is not always demonstrable morphologically in the presence of azotemia. (I do not refer here to those changes in structure which are commonly seen in patients who are afflicted with long-drawn-out and devitalizing illnesses.) Extensive lesions are commonly present, however. The mechanism of production of such lesions and/or functional disturbances seems to be intimately associated with increased protein destruction, with alkalosis, with hypochloremia, with low pressure in the small peripheral arteries, with dehydration, with decreased flow of blood and with diminished volume of blood. The most important of these seem to be dehydration and diminished blood volume, and in certain quarters the entire concept of the disease is being built on these two factors. The cause of all of this disturbance is apparently obscure; it is undoubtedly a toxin, the origin of which is most likely to be found in disorder of the intestinal tract, in bacterial infection, in autolysis of tissue or in combinations of these with each other or with even more obscure factors.

CLINICAL VALUE OF TESTS OF RENAL FUNCTION AND OF ESTIMATIONS OF THE EXTENT OF AZOTEMIA

For scientific purposes estimations of renal function in cases of biliary obstruction are most valuable, as they indicate disturbances which otherwise are not demonstrable. Abramson, in 15 cases of jaundice due to various causes, was not able to discover clinical evidence of impairment of renal function by estimations of the nitrogen, water or salt content of the blood or by determination of the ability of the kidneys to excrete phenolsulfonphthalein. Haessler, Rous and Broun, Hanner and Whipple, Moller and Lunsgaard, Chabanier and Gaume, Wakefield, Power and Keith, Nolhard and Fahr and others have worked on this problem and have been rewarded with varying results, none of which is decisive enough to be of clinical or scientific value. The truth of the matter seems to rest on the extraordinarily large reserve and recuperative power of the liver and kidney, and, as has been pointed out so many times, a decisive answer is not available until practically all of the

reserve is gone and no power of recuperation remains. In addition, as I have pointed out, no single isolated determination is of value; what is of value is a succession of determinations in the same case, done with similar technic and by the same technician. In such a series the results tell much more accurately whether the process is progressive or regressive.

The renal complication, or rather, the stage in which combined hepatorenal symptoms appear, occurs most often in cases of jaundice; yet it occurs in cases in which jaundice is absent. Sometimes it is possible to detect the renal disturbance in its infancy. It is impossible to say to what stage the hepatic disturbance must progress before clinical evidence of renal involvement can be obtained by functional tests, which, up to the present writing, are notoriously unsatisfactory. However, as I have pointed out, the renal mechanism furnishes a satisfactory means of detecting any preceding change in the liver; any significant change in the kidney could, therefore, in properly selected cases be employed, other things being equal, as a measure of any otherwise unrecognizable disturbance in the liver. This is the value of tests of renal function in the presence of the hepatorenal syndrome.

SUMMARY

In clinical medical and surgical practice there is widespread distribution of hepatorenal symptoms and/or lesions. Such conditions are caused by various forms of poisoning; they may be associated with abnormal physiologic states; they follow various forms of disease due to obscure causes or to frank bacterial infection; they occur in association with disturbances of the ductless glands, notably with thyrotoxicosis, with mechanical obstructions of excretory passages or the sudden release of the same and, finally, with traumatic conditions, including mechanical destructive effects and the disintegrating effects of chemicals or heat.

One cannot escape the conclusion that the association of hepatic and renal pathologic conditions of the human body is almost necessarily frequent, because of the primary essential fact that the two organs are the chief means of excretion after metabolic change has taken place; because one of them, the liver, is the chief agent for neutralization of poisonous chemical bodies absorbed from the alimentary tract, either introduced as such through its portal of entry or elaborated within its length during the process of digestion; because the portal area is important in the destruction of bacteria and the detoxification of bacterial toxins; because the second of these organs, the kidney, is the chief means of elimination of poisonous bodies which the body finds it impossible to neutralize; because the kidney takes on the eliminatory

function of the liver when the excretory passages of the liver become incapable of functioning (by mechanical blockage, inflammatory swelling, or destruction of the secreting layer of cells), and because the kidney excretes living bacteria from the blood stream.

It seems that in all of the conditions hereinbefore detailed the two essential factors in the syndrome under discussion—hepatic and/or renal symptoms and/or lesions—do not occur in every case and do not always occur in the same intensity and proportion. They occur, however, sufficiently commonly in every variety discussed to make it fairly certain that the hepatorenal symptoms and/or lesions occur as a consequence of more than one essential cause.

One is compelled to conclude that whatever the beginning and development of the hepatic lesions and their concomitant, subsequent or (rarely) preceding renal lesion may be, the ultimate generic cause is a poisonous body of some kind, which passes through the liver and kidney. Such a poison may arrive from an exogenous source or develop within the body. It may be an effect of chemical drugs and poisons, a toxin resulting from bacterial growth or a product of destruction of the various tissues of the body. It may be formed during metabolism or may be split off as a side product of digestion. Whatever the poisonous body may be, it has the same action on one or both of these two extremely important excretory organs. Sometimes a similar action takes place on other parenchymatous organs. Frequently secondary toxic bodies are formed, more often in the liver than in the kidney, having been manufactured during the disturbance, or (being already domiciled there but unneutralized) having been activated by the disturbance, which adversely affects the liver and engages the kidney in similar degenerative and necrotic changes. There are demonstrable pylogenetic reasons for this peculiar complementary nature of the clinical phenomena and the anatomic manifestations.

Once this train of functional and anatomic disturbances begins, other factors come into play, such as fever, shock, autolysis of tissue, anoxemia, anhydremia and azotemia. All of these aid and abet the primary agents or even each other, by producing conditions which are capable of creating, or are found associated with, similar cellular degenerations in these parenchymatous organs. As must be apparent, the amount of overlapping in the various manifestations of all the conditions discussed is enormous. A vicious circle, therefore, is produced, and the primary injury is enormously accentuated.

The differences in duration of the development of this clinical complex, in the symptoms, in the suddenness and dramatic effect of the clinical manifestations and in the rapid culmination in death, the more protracted course or the occasional—or, perhaps, more frequent than

is believed—recovery, seem to have important relations to the size of the dose of the causative agent, to the time limit in which the latter is delivered and to various forms of preceding sensitization of the body to diverse toxic bodies. This seems to be the correct view of the whole question of hepatorenal involvement.

There seems to be no biologic or clinical connection between the hyperpyrexia or so-called liver death and the protracted form of disease of the liver and kidney, the so-called hepatorenal syndrome. Liver death is probably related to some form of hyperacute bacterial infection. The hepatorenal complex reviewed and discussed in this communication seems to be something entirely different.

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EFFECTS OF HEMORRHAGE AND OF TRANSFUSION ON THE BLOOD FLOW IN AN EXTREMITY

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The relation between the blood pressure and the peripheral flow of blood is of interest in view of certain recent opinions on the mechanism of surgical shock (Freeman,[1] Meek,[2] Roome [3]). It has been suggested, and supported to various extents, by these authors that shock arises by the following mechanism: A marked reduction of the peripheral flow occurs as the result of a diminished blood volume and/or sympathico-adrenal activity; this ischemia produces capillary injury, with increased permeability, permitting a generalized loss of blood plasma, which finally progresses to peripheral circulatory failure.

Poiseuille and others [4] have exhaustively studied the relation existing between the head of pressure (P) and the volume flow (F) of homogeneous fluids in small rigid tubes. Under these conditions F is proportional to P, the ratio P/F is a constant and the relation is graphically linear. These observations, however, cannot be directly applied to the flow of blood in the peripheral circulation, because of the distensibility of the vessel walls and the corpuscular nature of the blood. Further modification of the relation may be anticipated in the intact animal during hemorrhage or shock (and in certain other conditions), owing to vasomotor activity and to changes in the blood concentration.

Previous studies of the P/F relation in the peripheral circulation have given somewhat divergent results. Whittaker and Winton [5] described it as linear and reported that the flow of blood in an isolated limb became zero at pressures of 20 to 30 millimeters of mercury and below. Norris, Bazett, and McMillan [6] described F as proportional to

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$P^{3/2}$ rather than directly, and Barcroft and Samaan [7] represented graphically a similar nonlinear relation.

In the present experiments the effect of graded hemorrhage on the blood pressure and the peripheral blood flow was studied in the intact animal. In some cases the effect of replacement of the blood was observed.

METHODS

The femoral blood flow was measured for 7 dogs anesthetized with pentobarbital sodium, by means of a photoelectric strohmuhr.[8] The blood pressure was measured by a mercury manometer at the inlet to the limb (distal to the strohmuhr). The

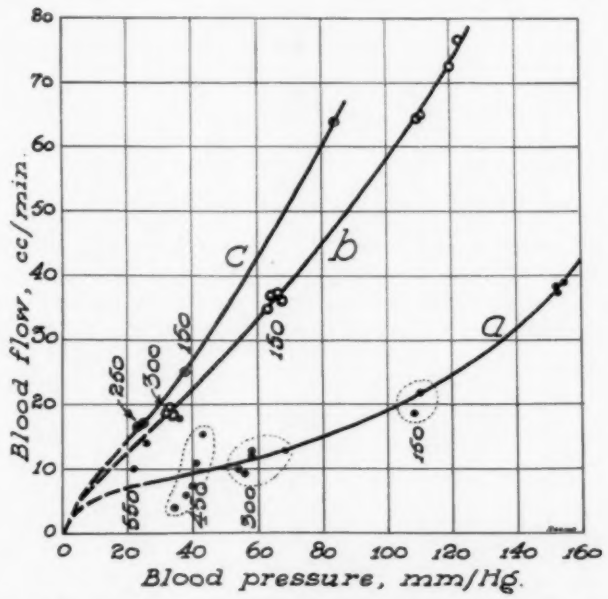

Chart 1.—P/F relations in the intact hindlimb of dog 13 (weight 10.5 Kg.). Curve *a* shows the first curve obtained, curve *b* the effect of exsanguination and transfusion and curve *c* a third graded hemorrhage after denervation. The numbers beside each curve indicate in cubic centimeters the amount of blood withdrawn.

blood pressure was lowered by graded hemorrhage, and in 3 cases the blood was replaced after the pressure had fallen to levels of 20 to 40 millimeters of mercury. In 3 experiments the limb was acutely denervated by section of the sciatic and femoral nerves. In 1 experiment the animal was exsanguinated as completely as possible and the blood replaced just before death; this was thought to represent an exhausted state, probably with marked atonicity of the vessels of the limb and with nearly maximal blood dilution. Two experiments were made with the use of saline solution from a reservoir to perfuse an isolated limb.

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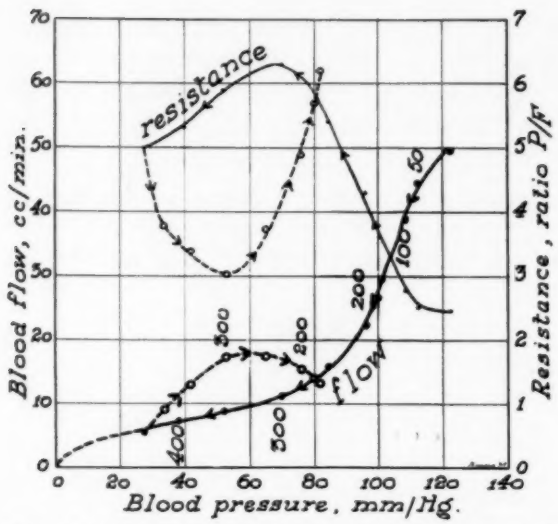

Chart 2.—P/F relations and numerical values for this ratio in dog 26 (weight 15.5 Kg.), acutely denervated. Note that on transfusion (broken line) the flow is greater and the ratio correspondingly less than during graded hemorrhage (solid line). The numbers beside the curves indicate the blood deficit, in cubic centimeters.

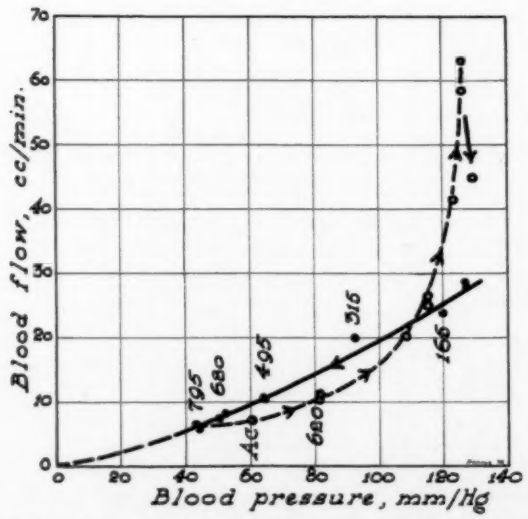

Chart 3.—P/F relations in dog 43 (weight 19.7 Kg.), showing the effect of hemorrhage (solid line) and of transfusion (broken line). Note that in this case the curve of transfusion fell below the curve of hemorrhage. The blood deficit is indicated in cubic centimeters; at *Ac*, 140 cc. of 10 per cent gum-saline solution (acacia) was given.

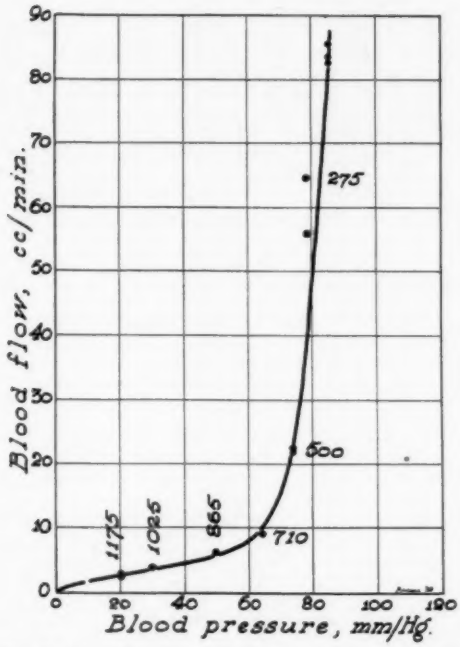

Chart 4.—P/F relations for dog 43, third curve, after denervation. Note the exceedingly low rates of flow with lowered pressures in this exhausted preparation.

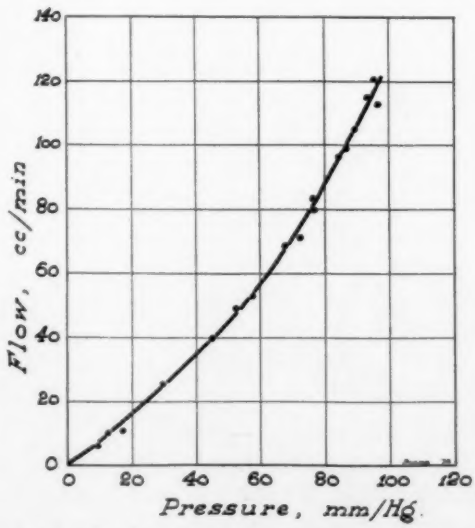

Chart 5.—P/F relations with saline perfusion of an isolated hindlimb (dog 15).

OBSERVATIONS

Typical curves showing the P/F relations in the intact limb are given in charts 1, 2, 3 and 4. In chart 1 it will be seen that the readings for a normal limb may be widely dispersed, particularly at the lower levels, and it is difficult to fit a curve to them. Smoother curves were obtained in the "exhausted" state and again after denervation.

The effect of replacement of the blood is variable. Chart 2 shows that the flow was abnormally great when the transfusion was begun and then fell off to about the expected level. Chart 3 indicates that the flow was less than expected and then rose above the previous curve. Chart 4 represents an experiment on the same animal which yielded the record shown in chart 3, with a second bleeding and transfusion intervening, and shows the excessively slow flow which occurs in some cases at low pressures.

The relation existing in the isolated limb when perfused with saline solution is shown in chart 5. It will be noted that this is a smooth curve, the characteristics of which fit fairly well the formula $F = m.P^n$, the values for n varying in different portions of the curve from 1.21 to 1.46.

COMMENT

The relation between the inlet pressure and the volume flow of blood in a limb of an intact animal during graded hemorrhage is thus an irregular curve and the ratio P/F a variable, tending (chart 2) first to increase as the pressure falls and then to diminish with further reduction of the pressure.

The explanation of the irregular relation no doubt depends on the interaction of the several factors mentioned previously as capable of distorting the linear relation of Poiseuille. First, because of the distensibility of the vessel walls, their diameter will increase with increased pressure, and the flow will be greater than the expectation from Poiseuille's law. Thus the ratio P/F will diminish as P increases, and the relation will be graphically expressed as a curve. Second, because the blood is a suspension of corpuscles relatively large in proportion to the smallest of the vessels they traverse, it would be possible that at low levels of pressure the volume flow would be abnormally reduced, producing further deviation from a linear relation. Third, in the intact animal during hemorrhage, since vasoconstriction occurs in response to the lowered blood pressure, further reduction of the volume flow at given values for pressure would result. These factors would all tend to reduce the flow at a given pressure below the expected level.

Two other factors tend to increase the flow at given pressures, thus opposing the three previously mentioned. These are, first, dilution of the blood by influx of fluid from the tissues in response to the bleeding,

which lowers the viscosity of the blood and increases the flow, and second, local dilatation or reactive hyperemia in response to the partial ischemia of reduced flows. It would seem that these factors would become important chiefly after there had been a considerable reduction of the blood pressure and of the blood flow. They would thus result in a diminution of the ratio P/F at the lower levels of P and F. That this occurs is well illustrated in chart 2, in which the ratio increases as the pressure falls, reaching a maximum at about 70 millimeters of mercury and then falling off as the pressure falls further.

For these reasons, then, the peripheral flow is markedly reduced with moderate blood losses and with slight depressions in the blood pressure. The flow then continues to fall slowly with further hemorrhage, while the blood pressure falls relatively rapidly. This correlates well with the finding of Blalock [9] that the cardiac output falls more rapidly than the blood pressure in response to hemorrhage. Exceedingly low levels of flow occasionally occurred with the lowered pressures (as shown in chart 4), but in no case did the flow entirely cease at the pressures studied. These reduced flows, which were only a few per cent of the normal, would constitute an essentially complete ischemia in the tissues, which supports the theory of the causation of shock previously outlined.

The effect of transfusion was variable, apparently depending on the degree of ischemia and the period for which it had been present, being distorted from the curve of hemorrhage by dilution and dilatation when the ischemia was marked and by constriction when it was less marked. It is of interest that in the experiment graphically shown in chart 2 both P and F were lower at the same levels of blood deficit during the transfusion than during the bleeding.

The relation of pressure to flow with perfusion of an isolated limb with saline solution was shown to approximate the formula $F = m.P^n$ when n is from 1.21 to 1.46.

SUMMARY AND CONCLUSIONS

The relation between pressure and flow in the peripheral circulation of dogs was studied and found to be an irregular curve. A marked diminution of flow occurs with moderate hemorrhage. This finding, with the observation of excessively retarded flow in some cases, lends support to the ischemic theory of shock.

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TOTAL PNEUMONECTOMY

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AND
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It is our purpose in this paper to report 2 cases in which total pneumonectomy was performed and to call attention to factors which may make for better results in the performance of an often difficult operation.

REPORT OF CASES

CASE 1.—D. C., a white man aged 42, a manual laborer and plumber, was admitted to the service of Dr. S. A. Lowenberg on May 4, 1936. The chief complaint was sharp pains in the lower part of the chest, on the left side. The patient had been well until two and one-half months before his admission to the hospital, when the pains referred to were noted. These were accompanied by cough, especially in the morning, productive of small amounts of foul-smelling and foul-tasting blood-tinged sputum. In the past eight weeks he had lost 24 pounds (10.9 Kg.). Night sweats had been present for three weeks. Dyspnea and palpitation were noted on exertion. The patient had been treated for addiction to morphine fifteen years ago. The family history revealed that a brother of the patient had died of cancer of the lip.

Physical examination showed a well nourished man who was not acutely ill. The chest was thin, with prominent supraclavicular fossae. An inspiratory lag and limitation of movement on the left were noted. Tactile fremitus and vocal fremitus were absent in the lower left quadrant of the chest posteriorly. Breath sounds were absent in the same area. A pleural friction rub was present at the base of the left lung anteriorly. At the apex of the heart was a soft mitral systolic murmur, not transmitted. The blood pressure was 112 mm. of mercury systolic and 70 diastolic.

A roentgenogram of the chest, taken on the day of admission, showed compensatory emphysema of the right lung, with flattening and compression of the right side of the diaphragm. The heart was not enlarged but was pulled over to the left. The left side of the diaphragm was obscured, and the position of the gas bubble in the stomach indicated that the position of this organ was higher than normal. There was atelectasis of the lower lobe of the left lung, with narrowing of the intercostal spaces in the left lower quadrant of the chest. There was no evidence of tuberculosis. The diagnosis was atelectasis of the lower lobe of the left lung, due to bronchial obstruction, inflammatory or malignant.

Bronchoscopic examination on May 6, by Dr. W. F. Moore, showed the left main stem bronchus below the opening of the bronchus of the upper lobe almost completely blocked by a new growth of tissue, which seemed to have its origin on the inner side. In this region the mucous membrane bled easily on touch. A

section was taken for laboratory examination. This had the clinical appearance of a bronchogenic malignant tumor, involving the left main stem bronchus below the level of the upper bronchus.

Microscopically the hyperplastic mucosal epithelium of the bronchus merged with the tumor, which formed irregular sheets of poorly differentiated prickle cells averaging less than one mitotic figure per high power field. There was

Fig. 1 (case 1).—Photomicrograph (× 115) showing the epithelial lining of the bronchus and also a squamous cell carcinoma. The carcinoma has formed islets and has invaded lymphatic spaces.

permeation of some mucosal lymphatics (fig. 1). The diagnosis was squamous cell carcinoma, type 3, of the bronchus.

On May 16 the patient was discharged to the radium clinic, where he received a course of six high voltage roentgen treatments, with appreciable benefit.

On June 1 the patient was readmitted to the hospital, to the surgical service of Dr. Moses Behrend. The temperature on admission was 102 F., but the patient did not appear acutely ill. The physical findings were essentially as before. On June 1 an initial pneumothorax was performed on the left side. A refill of 300 cc. was given. On June 3 a refill of 400 cc. was given. On June 5 a transfusion of 500 cc. of blood was given. On June 8, 200 cc. of air plus 50 cc. of 1 per cent peptone beef broth bouillon was injected into the pleural cavity. On June 10 an air refill of 250 cc. and a blood transfusion of 350 cc. were given.

On June 11 operation was performed with the patient under combined avertin with amylene hydrate and cyclopropane anesthesia. With the patient lying on the right side, incision was made over the third interspace on the left, from the sternum to the midaxillary line. The fibers of the pectoralis major muscle were cut across. The internal and external intercostal muscles were cut, and the pleura was opened in the third interspace. The upper lobe of the left lung was found to be almost completely collapsed as a result of the pneumothorax. The lower lobe was densely adherent, especially posteriorly and on its diaphragmatic surface. The hilar lymph glands were enlarged. Separation of these adhesions was extremely difficult and tedious. The mediastinal pleura was incised, and the left pulmonary artery and vein were ligated with silk. Despite this, considerable hemorrhage was encountered when an attempt was made to dissect out the left bronchus. The pedicle tourniquet of Carr was applied, and the lung was removed. At this point the patient's blood pressure fell sharply. Intravenous dextrose plus 350 cc. of blood was administered. Considerable free motion of the mediastinum was noted. The wound was closed with three heavy braided silk pericostal sutures. A small rubber drain tube was inserted in the eighth interspace. The patient left the operating room in grave condition and died shortly after returning to bed.

Summary.—In this case we were confronted with an inoperable condition. In view of the adhesions and the presence of carcinoma in the hilar glands, the operation should have been limited to exploration and biopsy.

Case 2.—H. S., a white man aged 40, was admitted to the service of Dr. H. B. Shmookler on June 30, 1929, because of pain in the right side, excessive cough and expectoration with hemoptysis.

The family history disclosed nothing of importance. The patient had had rheumatic fever in 1917, with recurrent attacks in 1921 and 1923. A chronic cough with much expectoration had been present for the past fifteen years. The history of the present illness showed that on June 28 the patient was awakened by cough accompanied by hemoptysis of approximately 200 cc. On June 29 there was a recurrence of hemoptysis, amounting to 120 cc.

Physical examination on June 30 revealed a well nourished man. Examination of the chest showed the breath sounds suppressed and distant on the right side and normal on the left. Urinalysis and chemical studies of the blood gave negative results. The Wassermann reaction for syphilis was negative. The sputum showed no tubercle bacilli. The clinical diagnosis was bronchiectasis with ulceration.

Roentgen examination revealed an extensive pathologic process at the base of the right lung and below the ninth rib, with densely thickened pleura and pleural effusion. The lungs showed moderate peribronchial fibrosis throughout. The left side of the diaphragm was depressed; the right side of the diaphragm was completely obscured. The heart was slightly retracted to the right. Injection of iodized poppyseed oil 40 per cent into the middle lobe showed no abnormalities. The bronchi of the lower lobe were not filled.

The patient was readmitted on June 27, 1937, to the service of Dr. A. Trasoff because of hemoptysis of approximately 200 cc. While in the hospital he had two other periods of hemoptysis, in which equal amounts of blood were produced. Bronchoscopic examination by Dr. Lell at the time of this admission revealed the trachea completely filled with foul-smelling pus. On aspiration this was found to be emanating from all the bronchi on the right side. The left side was clear. A great deal of granulation tissue was present in the bronchi on the left, which bled easily on the slightest touch. Prior to this admission the patient had been receiving regular periodic bronchoscopic aspirations at another hospital. After this admission he was given such treatment at frequent intervals.

Fig. 2 (case 2).—Photomicrograph (× 5) showing a large, dilated bronchus with infiltration of the mucosa and wall by acute and chronic inflammatory cells. Note the areas of superficial mucosal ulceration.

Roentgen examination at this time showed increased density on the right side, extending from the apex to the base of the lung. There was marked fibrosis, probably with bronchiectasis, in the base of the left lung. The heart and trachea were retracted to the right.

The diagnosis was: atelectasis of the right lung, cavities in the upper lobe of the right lung, probably due to suppuration; fibrosis with probable bronchiectasis in the lower lobe of the left lung; retraction of the heart and the mediastinal contents.

The patient was seen at weekly intervals in the bronchoscopic clinic, where aspiration was carried out. He was readmitted to the hospital on November 8,

at which time hemoptysis had recurred; hemoptysis was present on admission. Cough and expectoration had increased since the last admission. On successive days the patient had hemoptysis of 120, 60, 200 and 540 cc. This condition was treated by blood transfusions at regular intervals. The sputum at this time was profuse and foul-smelling. Sixteen ounces of sputum in twenty-four hours was the average output. The patient was miserable and begged that something be done to relieve him.

Surgical consultation was held with Dr. Moses Behrend. The gravity of the situation from a surgical standpoint, in view of the long-standing suppurative disease, was noted. However, it was felt that total pneumonectomy offered the only

Fig. 3 (case 2).—Photomicrograph (× 100) showing the wall of one of the abscess cavities. The section itself shows dense infiltration by polymorphonuclear cells. Immediately beneath but not shown in the section is infected granulation tissue.

chance for return of health. This operation was advised. Artificial pneumothorax was not even attempted, as it was felt that there was no free pleural space. This was confirmed at operation.

On December 10, with the patient under intratracheal cyclopropane anesthesia, an incision was made (by Dr. J. Sigafoos), curving under the right breast. A skin flap was turned back so as to expose the pectoralis major muscle, which was incised in the third interspace, the incision being carried backward to the posterior axillary line. The third, fourth and fifth ribs were sectioned through their costal

cartilages. The pleural cavity was opened in the third interspace. The lung was found to be densely adherent in practically every portion to the parietal pleura. By gentle dissection it was freed at the apex and gradually was partially freed from the diaphragm, where it was so densely adherent that at one point the diaphragm was torn in separating it. This tear was repaired immediately with a catgut suture. The vessels of the hilus were then attacked, and effort was made to ligate them individually. However, adhesions at the hilus were so dense that this became practically impossible. Profuse bleeding occurred during dissection, and it was necessary to apply large curved clamps to the hilus to control hemorrhage. It was impossible to make use of the hilar tourniquet, because of the

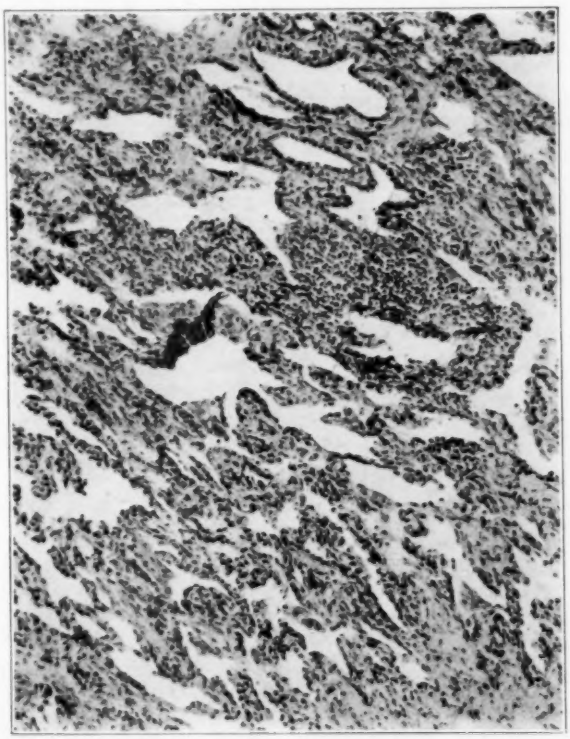

Fig. 4 (case 2).—Photomicrograph (× 100) of an area of atelectatic lung, showing the bronchi and alveoli lined with altered epithelium. Note the replacement of many intervening alveoli by fibrous tissue and infiltrating chronic inflammatory cells.

adhesions. At the time the hilar structures were clamped a sharp drop in blood pressure occurred, and spontaneous respiratory movements ceased. The operation was temporarily halted, and full control of the patient was given to the anesthetist. After approximately ten minutes of artificial respiration spontaneous respiratory movements were instituted, and the blood pressure rose to a normal level. The operation was then completed by ligation of the vessels and the major bronchi with heavy catgut sutures. The hilar structures were then oversewn with a small amount of lung tissue which remained. At the time of operation it

appeared that the bronchus had been occluded close to the carina. This proved subsequently to be untrue. A stab wound was made in the eighth interspace in the axilla, and a soft rubber tube was inserted. The wound was closed in layers after the third and fourth ribs had been approximated with heavy braided silk pericostal sutures. The patient left the operating room in good condition. He was returned to his bed and immediately placed in an oxygen tent. A blood transfusion was given.

On December 12 the patient was not dyspneic. A transfusion of 500 cc. of blood was given. On December 12 respiration was more labored. Aspiration of the chest through the tube was done, and 150 cc. of brownish red fluid was obtained. Two hundred and fifty cubic centimeters of blood was given by transfusion. On December 13 respirations were moist and labored. A laryngoscope was passed by Dr. J. G. Sirken, and the trachea was aspirated, with immediate relief. This aspiration was repeated with good effect on the following day. Thereafter it was not necessary. The patient did well until December 28, at which time a bronchial fistula developed, with immediate increase in the amount of sputum. On Jan. 3, 1938, in an effort to locate the site of the fistula, a small incision was made with the region under local anesthesia. At this time some necrotic particles of lung tissue were removed. The fistula was in such a position that it could not be reached at this time. A rubber tube was reinserted for drainage.

On January 11 there was a sudden attack of coughing accompanied by expectoration of 3 ounces (30 cc.) of blood. The following day there was a sudden large hemoptysis, during which the patient died. Postmortem examination revealed a small bronchial fistula arising from one of the bronchi of the upper lobe. There was a piece of the bronchus of the lower lobe, approximately 4 cm. in length, remaining. To this was attached a piece of collapsed lung tissue representing a small portion of the lower lobe. When this bronchus was opened it was found to be filled with blood which apparently arose from the mucous membrane. The mucous membrane was of the hyperplastic type described at the time of bronchoscopic drainage.

Summary.—This case presents another patient on the borderline of operability. Inflammatory disease of the lung was of long standing, and normal landmarks were obliterated; this prevented accurate dissection of the bronchus. However, we feel that if that portion of the bronchus that was inadvertently left behind had been removed, the patient would have made a good recovery.

PREOPERATIVE CARE

The success or failure of any operation may depend on the presence or absence of some well laid plan of attack. An operation of such magnitude as complete pneumonectomy cannot be undertaken haphazardly, and proper preoperative management is an important factor in the achievement of a successful result. As time goes on and greater experience is gained in the experimental laboratory and the operating theater we will continue to improve our results. At present we feel that certain measures are of definite value.

Preoperative blood transfusion is of value in this as in other surgical procedures when the figures for hemoglobin and for the total count of red blood cells are lowered. Hemoptysis is commonly associated with suppurative disease of the lungs and bronchi and is often the

presenting symptom in cases of malignant tumor. Pulmonary suppuration of even short duration usually causes some degree of secondary anemia.

Artificial pneumothorax is an important preliminary adjunct to operation and should be instituted seven or eight days before operation is performed, if possible. It is an aid at times in the localization and diagnosis of intrathoracic neoplasm. In the presence of suppurative disease it may decrease the amount of purulent material in the lung, lessening the likelihood of spill to the contralateral side at the time of operation. Furthermore, the patient becomes accustomed to a lower vital capacity, and the intrathoracic pressure approaches that which will be present at the time of operation. When the mediastinum is mobile, artificial pneumothorax will cause a gradual displacement which may be compensated for rather than a sudden one which may embarrass the circulation. Increased expansion of the contralateral lung occurs. the better to carry out the respiratory function, and here again the prospective postoperative physiologic condition is approached.

In addition to preoperative artificial pneumothorax, Rienhoff [1] has advocated the introduction of a solution of peptone into the thoracic cavity preoperatively in order to stimulate the formation of an exudate which might later organize and aid in the obliteration of the space remaining after removal of the diseased lung. The injection was carried out in our first case but not in subsequent cases. Our present attitude is that such injections are not requisite, for reasons which will be discussed under postoperative management. We know from the results of our experimental work that the space left by removal of a lung tends gradually to become smaller because of the enlargement of the remaining lung, because of the shift of the mediastinum to the side on which operation was done and because of a gradual natural collapse of the thoracic cage on the affected side, particularly in young persons. When the diaphragm is paralyzed by section of the phrenic nerve it rises and further helps to obliterate the space. If symptoms should develop as a result of absorption of the air left in the thorax at the time of operation, refills may be instituted at regular intervals. Finally, thoracoplasty may be performed to abolish dead space and is, in fact, obligatory if extensive infection of the pleural cavity has occurred as a consequence of operation.

Cooperation of the bronchoscopist is desirable in the treatment of patients whose clinical course has been characterized by expectoration of appreciable amounts of purulent sputum. Such patients should have the benefit of bronchoscopic aspiration immediately prior to surgical

1. Rienhoff, W. F., Jr.: The Surgical Technic of Total Pneumonectomy, Arch. Surg. **32**:218 (Feb.) 1936.

removal of the diseased lung tissue. Bronchoscopy is performed with the region under local anesthesia, and since nearly all patients have had previous therapeutic or diagnostic bronchoscopic examinations little additional mental or physical trauma is added to that of the major operation. The benefits of such preoperative treatments are obvious.

There has been a tendency, we feel, for bronchoscopists and clinicians together to continue for too long a period conservative treatment of patients who cannot permanently benefit from such treatment. Consequently the patients are often in poor physical condition at the time of operation and present an unnecessarily increased risk to the surgeon. At the time operation is performed it is found that irreversible intrathoracic changes have already occurred.

ANESTHESIA

In operations on the lungs the maintenance of a competent airway is a matter of paramount importance. For this purpose the use of the intratracheal tube is of great aid. When the maintenance of respiratory function depends on the integrity of a single main stem bronchus the normal margin of safety is immediately halved. Any spill of purulent or sanguineous secretion must be promptly aspirated during the course of the operation; otherwise symptoms of oxygen lack will soon appear and its effects on the cardiac muscle rapidly become evident. Breathing becomes forced. The respiratory movements are exaggerated, and the operative procedure must be delayed until they are once more quiet. If this condition is not promptly relieved, cardiac action increases in rapidity and in a short time may become irregular. The blood pressure falls, and suffocation is complicated by cardiac failure. These alarming manifestations may be prevented or promptly relieved by aspiration of the offending secretions through a thin catheter inserted through the intratracheal tube or beside it. In the case in which operation was performed for chronic suppurative disease of long standing the patient had expectorated from 30 to 250 cc. of sputum daily for at least fifteen years. Despite the fact that he had been subjected to bronchoscopic aspirations immediately prior to operation and several ounces of purulent secretion had been removed by this means, it was necessary to aspirate through the intratracheal tube at frequent intervals during the operation, and several ounces more of thick, tenacious mucopurulent sputum was recovered by this means. Had such a device not been utilizable, completion of the operation would have been impossible. In a lesser degree but in a no less important one such intratracheal control may become requisite in operations for malignant disease. Primary carcinoma of the bronchus almost invariably causes some bronchial obstruc-

tion, and with this occurs a damming back of secretions which frequently become purulent. Bronchiectasis and abscess of the lung occurring distal to the point of obstruction and secondary to bronchial carcinoma are usual rather than exceptional. One of the chief complaints of the patient operated on for malignant tumor was expectoration of foul-smelling sputum. During the manipulations attendant on removal of the offending lung these secretions can scarcely fail to be at least partially forced past the obstruction, after which they find their way to the trachea.

We believe the anesthetic of choice to be cyclopropane. Its skilful use enables the patient to maintain respiratory function by shallow, quiet breathing, which renders operation easier. The high percentage of oxygen available when cyclopropane is employed is an aid to more rapid readjustment of the oxygen saturation of the blood after the occlusion of one bronchus. In operations on the lung the appearance of cyanosis augurs ill, and in the presence of a competent airway it does not occur when cyclopropane is administered.

Burnett [2] has used local and regional anesthesia in the performance of pneumonectomy and has demonstrated its value. However, we feel that better control of the patient is obtained by means of intratracheal anesthesia.

The presence of an alert and competent anesthetist is most important at the time we choose to call the "critical period" of the operation. We refer to the moment at which the bronchus is clamped and the five minute period immediately following it. In experiments on dogs [3] we found that although the animal might be breathing quietly during manipulation of the lung and while the pulmonary vessels were being individually ligated, sudden occlusion of the main stem bronchus by a clamp usually resulted in a brief period of struggle, accompanied by respiratory and cardiac irregularity. From this the animals quickly recovered. A similar phenomenon occurs frequently but not invariably in man. One of us has seen 2 patients die within five minutes of the time of occlusion of the main stem bronchus, although their condition had been satisfactory before this time. In the case in which we operated for malignant disease no untoward reaction was observed. However, in the patient operated on for suppurative disease, when the bronchus was clamped the respiratory movements ceased, the cardiac action became irregular and the blood pressure promptly dropped to 70 mm.

2. Burnett, W. E.: One Stage Pneumonectomy Under Local Anesthesia: Successful Case Reported, J. Thoracic Surg. **6**:458 (April) 1936.

3. Behrend, A., and Mann, F. C.: Some Postoperative Effects of Pneumonectomy: A Morphologic Study, J. Thoracic Surg. **6**:685 (Aug.) 1937. Thomas, L. C.; Behrend, A., and Mann, F. C.: Experimental Pneumonectomy, ibid. **6**:677 (Aug.) 1937.

of mercury (systolic). The operation was immediately halted, and a hot compress was applied to cover the incision. The anesthetist was given complete charge of the patient. Respiration was maintained artificially with relaxation of the rebreathing bag attached to the anesthetic machine. Within five minutes the patient took his first voluntary inspiratory gasp. This was soon followed by a resumption of normal respiratory movements, and the blood pressure returned to its former level. The operation was carried on to completion without a further similar incident. We would stress particularly that it is important that the operation should be temporarily abandoned so that the anesthetist may have complete control of the patient. Too frequently a sudden cessation of respiration and rapid drop in blood pressure are followed by the trauma of additional operative procedures which are frequently hurried in an effort to complete the operation. This adds insult to the injury sustained, and frequently the patient is unable to withstand the added trauma.

OPERATIVE TECHNIC

We have found that the following position and incision give adequate exposure for removal of a lung. The patient lies on the back, the optimum position for anesthesia, on a small pillow placed so that the side to be operated on is raised off the table from 2 to 3 inches (5 to 7.5 cm.). The arms are both extended at shoulder height on armboards. Extension of the arm on the side of operation keeps it out of the way, raises the scapula on that side and enables the incision to be curved posteriorly. Extension of the arm on the opposite side makes it readily available for intravenous administration of fluids. This is usually begun early in the course of operation. Five per cent dextrose in physiologic solution of sodium chloride is given, and 6 per cent solution of acacia or citrated blood is given if the indications for it arise.

We prefer a parasternal flap incision curving under the breast and carried to the posterior axillary line. It allows closure of the wound in overlapping layers. The pectoralis major muscle is split over the third intercostal space. After the intercostal muscles have been divided the pleural cavity is entered and manually explored. If no contraindication to further exploration is encountered, the third, fourth and fifth ribs are sectioned at the costosternal border, and a self-retaining rib spreader is inserted. This gives a fuller view of the lung and mediastinum. The lung is then mobilized by being freed from any attachment it may have to the parietal pleura or to the mediastinum and by section of the pulmonary ligament. The pulmonary vessels are individually ligated, and the bronchus is clamped and cut separately. The importance of preserving a good blood supply to aid healing of the occluded bronchus has been demonstrated experimentally. If it is possible to

clamp the bronchus in such a manner that the bronchial vessels are not damaged, double ligation with braided silk will suffice. If the bronchial vessels are occluded by the clamps, the end of the bronchus should be closed with interrupted silk sutures. In any event it is most important to bury the bronchus by overlapping it with the adjacent pleura or any remaining lung tissue.

The greatest obstacle to careful operation and clean dissection is presented by diffuse adhesions to the pleural surfaces. Dense adhesions were present in both cases reported here, and the lung was separated with the greatest difficulty. Operability was doubtful in both cases but was nevertheless undertaken. In the first case it was necessary to pass a mass ligature with the hilar tourniquet, while in the second case the adhesions were so dense that it was impossible to apply the tourniquet and it was necessary to put several large curved hemostats on the hilus because of hemorrhage of alarming proportions occurring at the time of dissection of the hilar structures. It was impossible to dissect the right main bronchus as far as its bifurcation. Inability to do so led to the eventual death of the patient, for the autopsy specimen revealed the source of the final hemorrhage to be the mucous membrane of that small portion of the right main bronchus that remained as a result of the surgeon's inability to make a clean bronchial dissection. It is fully as important to know when not to proceed with total pneumonectomy as it is to understand the technic of the operation. In some cases inflammatory adhesions may be so great as to render continuation of the operation inadvisable. On the other hand, freeing of the adhesions in one stage and removal of the lung at the subsequent operation is a sensible procedure, particularly if the patient's condition at operation becomes in any way critical. In cases of malignant tumor, manual and microscopic examination (frozen section) of the mediastinal glands before removal of the lung is important. In our case of malignant tumor the carcinoma was observed to extend into the contralateral lung, but this did not become apparent until examination was made post mortem. Roentgenographic, clinical and operative examinations failed to reveal the presence of malignant disease in the "good" lung.

POSTOPERATIVE CARE

After the pneumonectomy the patient should be placed in a bed raised at the foot, so that his head is dependent. This position facilitates tracheal drainage and is an important factor in the prevention of an aspiration type of pneumonia or atelectasis attributable to bronchial plugging, particularly when cough is suppressed because of pain in the line of incision. Morphine and atropine may both be used judiciously. Pain is not commonly a prominent postoperative symptom. Atropine is

a double-edged weapon, and while it may have a brilliant effect in the abolition of minor degrees of diffuse pulmonary moisture it is of little value in the presence of large amounts of bronchial secretion. The formation of a more viscid bronchial content may even defeat the purpose for which the drug is given.

The oxygen tent is the greatest single postoperative aid at the surgeon's disposal. It is used regularly for at least the first seventy-two hours and may be used longer as indicated. Dyspnea is not a prominent factor after pneumonectomy; nevertheless, the oxygen tent is helpful in prevention of postoperative pneumonia and serves to allay apprehension, because respiratory function is facilitated and deep breathing is not required.

The values for hemoglobin and red blood cells are the best index to the requirement for blood transfusions. In the presence of postoperative shock, nothing equals the transfusion of blood as a means of restoring and maintaining a proper blood pressure. A transfusion of 500 cc. may be given with impunity and repeated as indicated.

The surgeon who is able to depend on the cooperation of a competent bronchoscopist is fortunate. In the case in which operation was performed for suppurative disease, tracheal rhonchi were a prominent and foreboding feature, commencing forty-eight hours after the operation. Other methods of relief failing, it was decided to undertake tracheal (not bronchial) aspiration. This was successfully carried out with the patient in bed. He suffered no distress and had immediate relief from symptoms, although recurrence the following day required another aspiration. After the second aspiration, relief was permanent.

Whether to drain or not to drain the thoracic cavity after pneumonectomy depends on conditions noted at the time of operation. If dissection of the lung has been difficult and if capillary bleeding uncontrollable by ligature has occurred, it is well to drain. The amount of blood lost is under constant observation and the need for its replacement can be anticipated. If tube drainage is employed it is not necessary to displace dressings to aspirate the chest of a patient who may be very ill. A second indication for drainage is obvious contamination by pus or by bronchial secretion. Drainage is best obtained by insertion of a soft rubber tube through a stab wound independent of the operative incision. The tube is attached to a glass adapter, and another tube carries the contents of the pleural cavity into a bottle, the end of the tube being under water in the bottle. This device maintains a constant negative pressure in the pleural cavity. The preferable method is to close the chest without drainage, and this may be done if removal of the lung has been cleanly accomplished.

Of great value is the use of the portable x-ray apparatus in observing intrathoracic adjustments as they occur after operation. Serial roentgenograms furnish invaluable aid in the postoperative treatment, for physical signs following such an operation are difficult to interpret.

COMMENT

It has been repeatedly demonstrated [3] in experiments on dogs that total pneumonectomy is well tolerated, that recovery occurs in approximately 90 per cent of the animals operated on, that the occluded main stem bronchus will heal and remain closed and that absence of one lung is compatible with a long life and a useful existence. While most of the aforementioned facts have been found to hold equally true for patients who have been subjected to pneumonectomy, the recovery rate in the experimental laboratory is higher than that in the surgical theater. It must not be forgotten, however, that the animals operated on are in good health at the time of operation, while patients come to operation after having harbored malignant or suppurative disease or both for some time.

The age of the patient and the length of time the disease has been present are of great importance in the prognosis. It is found with experimental animals that the best results are obtained in those which have not yet attained full growth. Similarly, it is noted that children generally respond well to lobectomy and pneumonectomy. This is doubtless attributable to several factors. In children disease has not been harbored so long that adjacent structures are markedly affected by the morbid process, and general systemic effects are not pronounced. Furthermore, in children the elastic fibers of the remaining lung have lost none of their functional elasticity, whereas among adult patients loss of pulmonary elasticity is common. Nor is the thoracic cage as rigid in the child as in the adult. This rather pliant thoracic cage allows expansion of the sound remaining lung, and at the same time offers greater opportunity for a natural collapse of the chest wall on the side on which operation is done, tending to produce a thoracoplasty in effect without recourse to operation.

INDICATIONS FOR PNEUMONECTOMY

Total pneumonectomy is indicated as the treatment of choice for squamous cell carcinoma and adenocarcinoma of the bronchus and lung. For the former therapeutic roentgen rays are of no value. For adenocarcinoma the value of irradiation is questionable, and while an occasional patient appears benefited, recurrences are the rule rather than the exception, even when a beneficent result seems to have been obtained. Total pneumonectomy for malignant disease has not been

done for a sufficiently long time or in a sufficiently large group of cases to permit one to judge whether the operative results are better than those of irradiation.

Total pneumonectomy is also indicated for diffuse chronic suppurative disease of one or more lobes of the lung, such as may occur in the presence of bronchiectasis, cystic disease of the lung and multiple chronic pyogenic abscesses. The operation is requisite if the disease is limited either to one lung or to single lobes of both lungs. The use of this operation in the treatment of apparent unilateral tuberculous disease of the lung does not appear justified because of the risk of the operation, because of the fact that other, less formidable operations offer benefit to tuberculous patients and because postoperative involvement of the contralateral side is a real danger. The single exception to this rule occurs in the presence of complicating bronchial stenosis of a type that is not relievable by endoscopic methods. Patients with this condition become chronic invalids because they are subject to rather frequent attacks of pneumonitis and atelectasis caused by the stenosis of the bronchus. The stenosis may occur as a result of healing of an intrinsic bronchial infection or may be dependent on occlusive pressure on the bronchus from without, the usual cause of such pressure being the presence of enlarged hilar lymph nodes.

It is important for the surgeon to know what constitutes a suitable case for pneumonectomy. In the presence of malignant disease of the lungs it must first be established that the disease is primary in the lung and not metastatic to it from some other source. Painstaking physical and roentgenologic examinations are necessary. In the presence of a primary carcinoma of the lung, evidence of extension to some other organ is sufficient to contraindicate radical operation. Enlarged supraclavicular nodes particularly should be sought and if found should be subjected to biopsy. If carcinoma is found, palliative treatment with roentgen rays alone should be used.

In many cases of primary carcinoma of the lung it will be found possible to decide the question of operability only after exploratory thoracotomy has been done. The presence of enlarged glands at the hilus is in itself no contraindication to proceeding with the operation, unless these glands are obviously unresectable. Inseparable adhesions of the lung to the surrounding structures and extension of the growth across the carina are valid reasons for withdrawing from further operative intervention.

In the presence of diffuse suppurative disease of the lung or of bronchial stenosis the question of operability must depend in a large measure on the physical findings and on roentgen examination of the lung that will remain to carry on the respiratory function. Any marked

disease of this lung precludes pneumonectomy but not necessarily lobectomy. One may not be able to decide the question of operability until the chest has been opened, although the results of preoperative artificial pneumothorax or an attempted artificial pneumothorax may give some hint. In 2 patients (both adults) we have seen the operation of pneumonectomy abandoned after little headway had been gained in prolonged attempts to free the lung from its adhesions to the hilus and parietal pleura. In both patients it would have been foolhardy to proceed with the dissection. Both recovered from the exploratory thoracotomy.

SUMMARY

Two cases in which total pneumonectomy was done are reported, with comment on preoperative care, methods of anesthetization, operative technic, postoperative care and indications for operation. Factors influencing the success of total pneumonectomy are reviewed.

RETROPERITONEAL LYMPH NODES

THEIR IMPORTANCE IN CASES OF MALIGNANT TUMORS

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From the point of view of malignant tumors metastasizing through the lymphatic channels or spreading from one group of lymph nodes to another along the lymphatic channels the retroperitoneal nodes are the most important lymph nodes in the body. Perhaps they are not involved as frequently as are the cervical nodes, but, as far as the relative effect on the general condition of a patient suffering from a malignant process is concerned, the retroperitoneal nodes are far more important than any other group of nodes. Owing to their relative inaccessibility little attention has been given them, and the relation between certain clinical symptoms and physical signs and pathologic involvement of this group of nodes is often overlooked.

ANATOMY OF THE ABDOMINAL AND PELVIC NODES

From an anatomic standpoint most of the abdominal lymph nodes are retroperitoneal, in that none of them are within the peritoneal cavity. In this sense, while these nodes are situated within the general boundaries of the abdomen, they are all extraperitoneal, but it has become a custom to call them retroperitoneal, and usage has established this expression.

The abdominal and pelvic lymph nodes form a continuous system, but for purposes of description they may be divided into two main groups: (1) the iliac nodes and (2) the abdominoaortic nodes. The second group of abdominoaortic nodes may be subdivided into: (1) the mesenteric group and (2) the para-aortic or, as it is sometimes called, the juxta-aortic group. The nodes which form these groups are all connected by lymph channels, and other channels bring to different parts of this extensive system of nodes lymph from the lower extremities and from all the organs and structures in the pelvis and abdomen. Lymph which has passed through these nodes passes thence mainly through the thoracic duct into the subclavian vein, but some of it passes upward through channels which connect the upper para-aortic nodes with similar nodes which follow the course of the aorta on the left side and of the inferior vena cava on the right side.

From the Section on Therapeutic Radiology, the Mayo Clinic.

Below the bifurcation of the common iliac vessels the iliac nodes are made up of two chains: (1) the external iliac nodes and (2) the internal iliac nodes. Above the point of junction of the external and internal iliac vessels the iliac nodes consist of a single chain of nodes accompanying the common iliac vessels to the bifurcation of the abdominal aorta and the inferior vena cava. The two chains of common iliac nodes then come together to form the para-aortic nodes.

The external iliac nodes receive lymph from the superficial iliac nodes, the deep iliac nodes, the lower extremities, the glans penis or the clitoris, the umbilicus, the lower part of the abdominal wall, the upper part of the vagina, the neck of the uterus, the prostate gland, the bladder, the membranous portion of the urethra and the internal iliac nodes. All this lymph then passes through direct channels communicating with the common iliac nodes and thence to the para-aortic nodes.

From the perineum, the main part of the urethra, the deep tissues of the posterior aspect of the thigh and the buttocks and the pelvic organs lymph passes along channels and through primary nodes along the anterior aspect of the sacrum and the middle hemorrhoidal vessels into the internal iliac nodes which accompany the internal iliac artery. Lymphatic channels communicating with the common iliac nodes then convey the lymph to these nodes, where it joins with lymph from the external iliac nodes; from the common iliac nodes other lymphatics convey the lymph to the para-aortic nodes.

The para-aortic nodes, numbering twenty-five to thirty (fig. 1), follow the course of the abdominal aorta and the inferior vena cava. Some of the nodes are on the right of these vessels, some on the left, some in front and some behind. All are rather large. Into the right para-aortic nodes flows lymph from the right common iliac nodes, the right testis or ovary, the right half of the uterus, the right fallopian tube and broad ligament, the right kidney and adrenal gland and nodes which accompany the lumbar arteries. Through communicating channels lymph may pass from the right para-aortic nodes to the nodes behind or in front of the abdominal aorta and to the receptaculum chyli. Into the left para-aortic nodes flows lymph from the corresponding organs and structures on the left side of the body.

Into the same group of nodes, especially those above the point of origin of the spermatic or ovarian vessels, a series of lymphatic channels on each side bring lymph directly from the right or left testis or ovary. These channels follow the course of the spermatic arteries in the male or of the ovarian arteries in the female. This explains why a malignant tumor of the testis or ovary which has not ruptured the capsule of the organ metastasizes first to these nodes. Metastasis to the inguinal nodes is a sign that the neoplasm of the testis or ovary has ruptured the capsule or that the lymphatics of the organ have an anomalous

arrangement. In the presence of tumor of the ovary rupture of the capsule is common, and owing to the situation of the organ this leads to rapid extension of the malignant process to the peritoneum and to other abdominal organs. This is not often true of tumor of the testis.

The anterior para-aortic nodes are situated in front of the abdominal aorta; some are at the point of origin of the inferior mesenteric artery, some are at the point of origin of the superior mesenteric artery, and some form an important group around the celiac axis. The group of nodes in the region of the celiac axis is situated behind the stomach

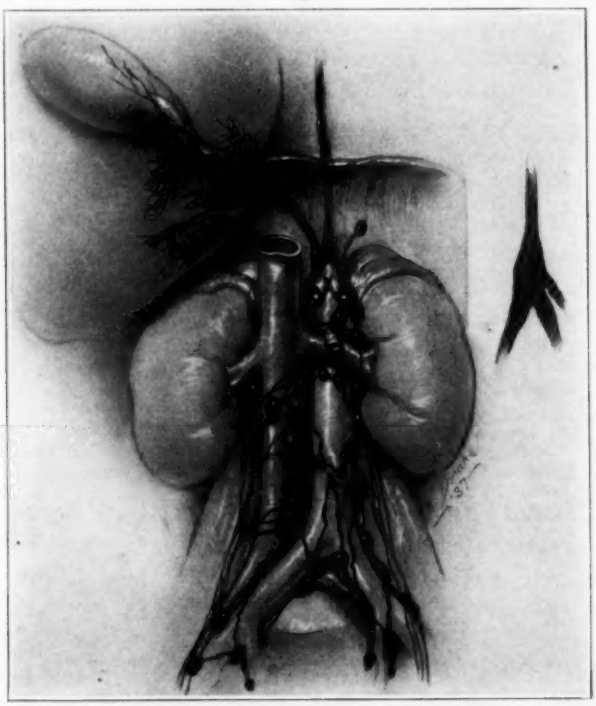

Fig. 1.—Para-aortic and iliac lymph nodes, into and through which flows lymph from the lower extremities, pelvis, pelvic organs, buttocks, small and large intestine, stomach, liver, kidneys, adrenal glands and spleen. The lymph from the testes or ovaries is carried through separate lymph channels directly into the upper para-aortic nodes in the region of the celiac axis.

and in close relation to the pancreas. Lymphatic channels carry lymph from the anterior nodes to the right and left para-aortic nodes, to the posterior nodes and to the receptaculum chyli. Other channels bring to the para-aortic nodes lymph from the stomach, intestines, liver, pancreas and spleen.

Along the greater part of the rectum, the descending colon and the splenic flexure (fig. 2) and along the branches of the inferior mesenteric

artery which supply these structures are situated nodes connected by lymphatic channels which unite to form larger and larger channels and through which lymph flows into the para-aortic nodes. Other nodes and channels which form part of the same extensive system are situated along the transverse and ascending portions of the colon, including the cecum and appendix, and along the entire length of the small intestine (fig. 3). Thence, following the branches of the superior mesenteric artery, they also convey lymph to the para-aortic nodes.

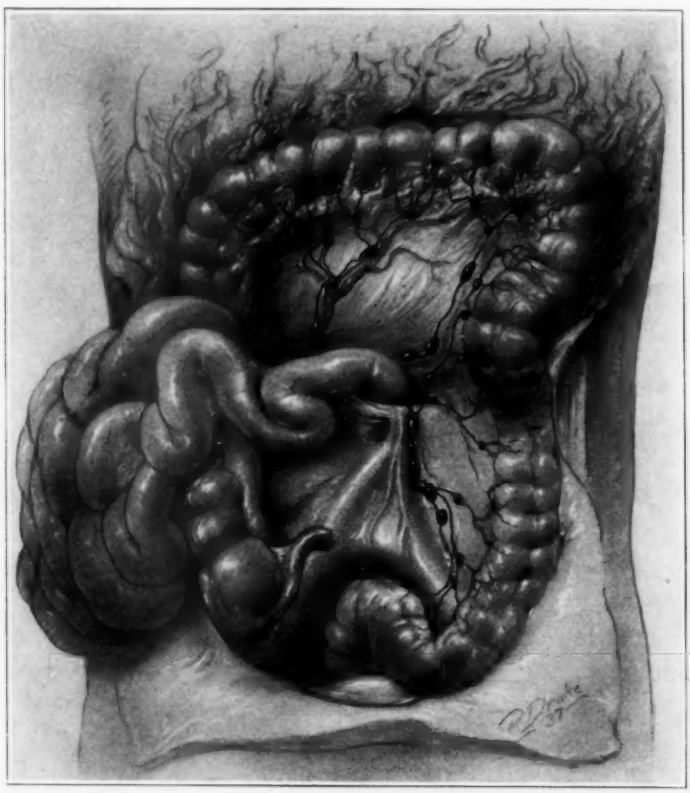

Fig. 2.—Lymphatic drainage of the rectum, descending colon and splenic flexure. Lymph from these structures is carried to the para-aortic lymph nodes.

Along the lesser and the greater curvature of the stomach, where they follow the course of the gastric or gastroepiploic arteries, are situated a series of nodes into which flows lymph from the superficial and deep coats of the organ. Through secondary communicating channels the lymph then passes into the group of para-aortic nodes in the region of the celiac axis. The lymphatic channels which drain the fundus of the stomach pass toward the left side and convey lymph to the splenic

nodes. Situated between the spleen and the pancreas and collecting lymph from both of these organs as well as from the fundus of the stomach, the splenic nodes follow the course of the splenic artery and also convey lymph to the para-aortic nodes. Following the course of the hepatic artery, of the portal vein, of the right gastroepiploic artery and of the cystic and common bile ducts, a series of nodes and communicating channels collect lymph from the liver and convey it to the upper or celiac group of para-aortic nodes.

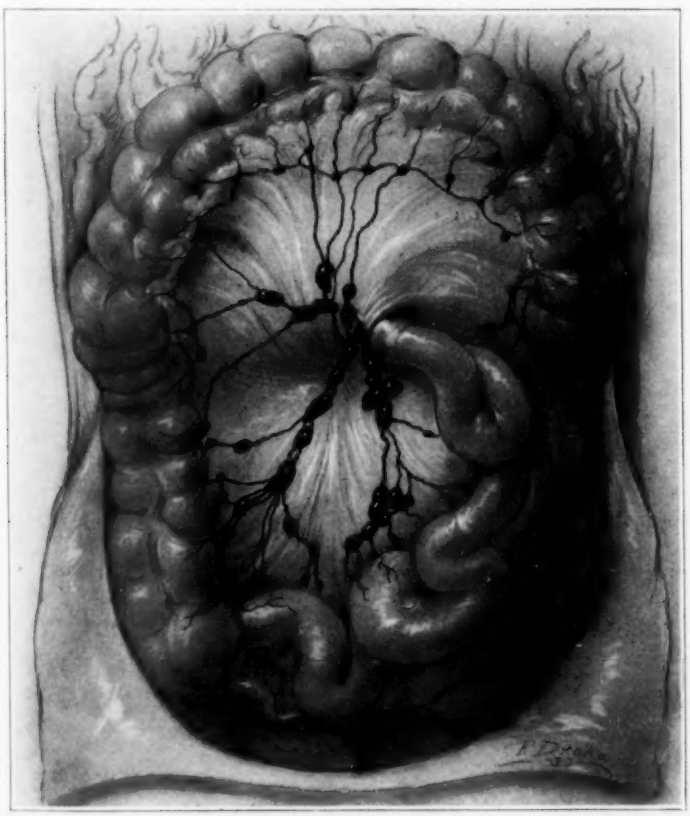

Fig. 3.—Lymphatic drainage of the small intestine, vermiform appendix and ascending and transverse portions of the colon. The lymph from these structures also is carried to the para-aortic nodes.

Besides these main groups of lymph stations, each abdominal organ has its own system of lymph channels and nodes through which the lymph passes on its way to the main collecting nodes in the para-aortic group. To attempt to describe in detail the lymphatic system of each organ would be to divert the attention of the reader from the main subject of this paper. What is essential to remember is that practically

all the lymph from the abdominal and pelvic organs, as well as from the lower extremities, must pass through the para-aortic nodes or through both the mesenteric and the para-aortic nodes. Casual reflection alone is sufficient to make one realize that groups of lymph nodes which drain so many important organs in the abdomen and pelvis must themselves be relatively important.

METASTASIS FROM CARCINOMA

Carcinoma of the bladder, prostate gland, uterus or rectum often extends backward (or outward and backward) along the lateral and posterior planes of the pelvis, where the main lymphatic channels and nodes are situated, frequently causing a dull aching pain in the sacral region. The malignant process may infiltrate some of the sacral nerves;[1] when this occurs the pain becomes much more severe. Not infrequently, especially in carcinoma of the prostate gland, the malignant elements find their way into the blood stream and thence to various bones or internal organs. The symptoms caused by the primary growth continue to increase, but to these are added the symptoms caused by extension of the tumor beyond the organ primarily affected.

Many patients who are known to suffer from carcinoma of the bladder, prostate gland, uterus or rectum or who have previously undergone partial or complete surgical resection of one or another of the organs mentioned consult a physician because for some time they have been distressed by fresh symptoms. These symptoms may be: pain in the back, pain in the abdomen, bloating and belching after meals, abdominal distention, increase in flatus, a sensation of undue fulness after eating (which the patients often describe as a sense of not having enough space for food), gradual increase in size of the abdomen or increasing constipation.

Backache.—In most cases the backache affects the lumbar region, but sometimes the sacral or the lower part of the thoracic region also is affected. In certain cases backache is absent but the patient complains of pain around one hip and down the corresponding thigh, around the knee or throughout the lower extremity. Sometimes the pain is felt chiefly, if not wholly, in one or both feet and only later extends to the knee, thigh or hip. Not infrequently the condition is mistaken for sciatic neuritis or sciatica, and the patient may be treated on this basis for some time, with little or no success. Pain in the lumbar region may not manifest itself for some time. The pain, which usually is a dull ache, often extends to one or both hips and down one or both lower extremities. Sometimes it gradually assumes a boring character; it may become so severe as to require opiates for relief.

1. Elaut, L.: The Surgical Anatomy of the So-Called Presacral Nerve, Surg., Gynec. & Obst. **55**:581-589 (Nov.) 1932.

When the pain is dull, roentgenographic examination of the spine and pelvis may not give the slightest indication of metastasis to these bony structures. Under these circumstances the patient's symptoms are probably due to metastasis of the tumor to the para-aortic lymph nodes or to these and the mesenteric nodes, and this possibility should always be kept in mind. The pain is probably due to the pressure of nodes enlarged by metastasis on nerves that enter into the formation of the lumbosacral plexus or on branches of this plexus which supply the hips and lower extremities. In favor of this view is the fact that suitable exposure of the lower part of the thoracic region and of the lumbar and sacral regions to converging beams of roentgen rays is often followed by partial or complete relief from pain, and the relief thus obtained may continue for weeks or months. Moreover, the degree of relief following irradiation is likely to be greater when the backache is dull than when it is severe and boring.

When the pain in the back is severe or boring, a roentgenogram of the spine and pelvis is likely to yield evidence of skeletal metastasis. Should this be absent, severe backache, with or without extension of the pain to one or both lower extremities, may be due to metastatic infiltration of the aforementioned nerves. In this event the prospect of relief from pain after roentgen treatment depends on the kind of tumor and its sensitiveness to irradiation and on how much the nerves have been injured. If the nerves have been injured beyond repair, an indication of the fact may be found in the complete lack of response to irradiation. If the neural injury has been only partial, roentgen treatment is likely to be followed by some degree of relief.

One factor which may have considerable influence on the action of roentgen irradiation is the site of the injury in relation to the region treated. Even when the pain is confined to the hip or the lower extremity (assuming that metastasis to the pelvic bones or to the bones of the extremity has been carefully excluded by roentgenographic examination), treatment directed to the hip or to any part of the extremity is not likely to have any effect on the pain. The treatment should be directed mainly to the lumbar region, but the lower part of the thoracic region and the sacroiliac region also should be irradiated.

Pain in the Abdomen.—When pain in the abdomen is the chief complaint, it usually assumes one of two forms; in one form the pain recurs at irregular intervals, tends to be slight or moderate at first, gradually increases in intensity for a variable period and then gradually subsides. It may last only a few minutes or may continue for a longer time, and it may recur at varying intervals. It often shifts from one part of the abdomen to another, but in some cases this tendency to shift is not a prominent feature. Week by week the pain increases in severity

and constancy. It is often associated with gradually increasing constipation. The impression is that of a spastic pain, probably caused by mechanical interference with the motor function of the bowel by gradual enlargement of the para-aortic nodes and perhaps also of the mesenteric nodes. The variations in the pain and in the other intestinal symptoms observed in different cases probably depend on variations in the anatomic relation between the nodes and the intestine, according to the particular nodes most involved and the part of the intestine affected.

The other form of pain occurs more or less regularly after meals and may thus suggest peptic ulcer. Intermittent at first, it gradually becomes more constant and is often accompanied by a sense of epigastric fulness after eating. As time goes on, the patient, in an effort to reduce the discomfort or pain caused by an ordinary meal, may acquire the habit of taking food in small quantities at frequent intervals. The pain, which may be a dull ache or soreness, is sometimes accompanied by nausea and vomiting.

Bloating and Belching—Flatus.—Bloating and belching after meals are common symptoms and are usually associated with the aforementioned sense of fulness in the epigastrium after eating. These symptoms gradually increase and are undoubtedly caused by crowding of the stomach and upper part of the small intestine by enlarging retroperitoneal nodes. The stomach and intestine can no longer expand as their contents increase; interference with peristaltic action probably causes abnormal delay in the emptying of the stomach and in the transit of food and gas through the upper part of the small bowel, and gas tends to accumulate. In some cases a gradual increase in flatus indicates interference with the normal function of the lower part of the small intestine and colon by mechanical pressure of nodes enlarged by metastasis of the tumor along the lower half of the abdominal aorta and sometimes also of the iliac nodes.

Enlargement of Abdomen.—An occasional patient complains of a gradual increase in size of the abdomen and is obliged to wear clothing of a larger size. Usually this enlargement of the abdomen is accompanied by bloating, belching and a sensation of undue fulness, weight and discomfort in the epigastrium, especially after eating.

Constipation.—Constipation is such a common complaint of persons who are otherwise well that little weight could ordinarily be attached to this widely prevalent disturbance by itself. However, when a person who is known to have had a malignant process and who previously has seldom or never been affected by sluggishness of the colon complains that for several weeks or months there has been a gradually increasing disinclination of the large bowel to evacuate its contents, it seems justifiable to suspect a mechanical cause. Moreover, when, as not infrequently

occurs, roentgen irradiation of the abdomen is shortly followed by recovery of normal intestinal function for weeks or months, the suspicion seems confirmed.

Physical Signs.—When a carcinoma of the bladder, prostate gland, uterus or rectum has invaded the retroperitoneal nodes, the physical signs may be so overshadowed or masked by those caused by the primary tumor or by extension of the growth to the abdominal structures and organs that a clear distinction between them may be difficult or impossible. Also when the primary neoplasm has been removed surgically and the symptoms mentioned arise later, the presence of local recurrence, with or without extension to various abdominal structures, may add a confusing note. In general, the physical signs related to the primary tumor or to local recurrence of the malignant process after an antecedent excision are rather definite. Confusion arises chiefly when metastasis to the peritoneum, intestine or liver has developed. Even though the physical signs are sometimes not clear enough to enable one to exclude metastasis to the liver, for example, they may be sufficient to indicate that the retroperitoneal nodes also are probably involved.

When the primary growth has been removed surgically and clinical evidence of local recurrence is lacking, the following physical signs increase the probability of metastasis to the para-aortic nodes:

Palpation in the epigastric and umbilical regions (and sometimes in the hypochondriac and lumbar regions as well) elicits a sensation of abnormal resistance. When the abdominal wall is obese or muscular or when the abdomen is distended with gas or fluid, perception of this abnormal resistance may be difficult. In the majority of cases, however, recognition of abnormal resistance offers little difficulty. Sometimes the resistance is greater on one side than on the other, and sometimes its distribution is fairly uniform. Sometimes it is confined to the upper half of the abdomen, and sometimes it extends downward as far as the iliac regions. In some cases a sensation of irregular nodules is obtained, but in others the resistance is diffuse and uniform. Moreover, the impression derived by palpation is that this abnormal resistance is rather deep. Usually the lower border of the liver, which falls and rises with respiration, can be distinguished clearly, but occasionally the retroperitoneal nodes are so large and closely packed and extend so far forward and upward that it may be difficult or impossible to be certain where the liver ends and the nodes begin. The same difficulty may arise when the liver also has been invaded by metastasis. When the para-aortic nodes are only slightly affected the sensation of deep resistance may be correspondingly slight and may be obtainable only by deep palpation on each side of the spine.

The second significant sign is slight or moderate tenderness when pressure is exerted on the deep resistance already described. Usually

this tenderness, while seldom pronounced, is definite and cannot be mistaken for the discomfort caused by pressure of the examiner's hand. Few patients have any difficulty in distinguishing between the two. When abnormal resistance is present and pressure is exerted, the patient says, "That hurts," winces or tries to draw away. When the abdomen is normal, on the contrary, the anterior abdominal wall can be depressed until it comes in contact with the great vessels and the spine, and the patient's only sensation is discomfort from the pressure.

TUMORS OF THE TESTIS OR OVARY

Lymph from the testes or ovaries normally drains not into the inguinal nodes but (through a separate system of lymphatic channels) directly into the upper para-aortic nodes. From this point the lymph may pass upward through the thoracic duct and empty into the subclavian vein on the left side, or on the right side (when a right lymphatic trunk is present) into the junction of the internal jugular and the subclavian vein. A tumor of the testis never metastasizes to the inguinal nodes unless it has perforated the capsule of the organ; in fact, extension of a malignant process from the testis to the inguinal nodes is an absolute sign that the tumor has broken through the capsule of the organ. In some cases of testicular tumor, metastasis to the para-aortic nodes may be accompanied or followed by metastatic invasion of the iliac nodes without involvement of the inguinal nodes. As the experimental studies of Jamieson and Dobson [2] have shown, this may be due to such effective blocking of the malignant process by the para-aortic nodes that the malignant elements are dammed back into the iliac nodes either through the usual channels or through collateral channels.

The most common malignant neoplasms of the testis, the embryonal carcinoma (or seminoma) and the mixed, or teratoid, tumor, are characterized by early metastasis—much earlier than is generally suspected. Moreover, the first site of metastasis from a tumor of this kind is almost always the para-aortic nodes, especially those above the point of origin of the spermatic or ovarian vessels. Later the malignant process may find its way through the thoracic duct to the so-called sentinel nodes in the supraclavicular region, may block the thoracic duct in the mediastinum and may thence spread outward to invade the lungs; or, having succeeded in running the lymphatic blockade of the para-aortic and sentinel nodes, the malignant cells may be thrown into the circulation and be scattered through the lungs, the brain or other organs. In many cases, however, the blockade offered by the para-aortic nodes prevents further dissemination of malignant cells for many months or for several years.

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2. Jamieson, J. K., and Dobson, J. F.: The Lymphatics of the Testicle, Lancet **1**:493-495 (Feb. 19) 1910.

Symptoms.—Metastasis to the para-aortic nodes is prone to give rise sooner or later to some of the symptoms which have already been described in connection with carcinoma of the bladder, prostate gland, uterus or rectum, and the gradual development of these symptoms should always make one consider the possibility of metastasis to the retroperitoneal nodes, which are the first station of drainage for lymph from the testis.

The same is often true of certain types of tumor of the ovary, but the tendency of many ovarian neoplasms to rupture the capsule of the organ and to spread over the peritoneum, where the malignant elements form innumerable implants or cause the omentum and coils of intestine to adhere to one another or to the pelvic structures, tends to confuse the clinical picture. Under these conditions, also, the prevalence of ascites adds another confusing factor.

Therefore, whenever a patient who is known to harbor a malignant tumor of the testis (or ovary) or to have had such a tumor removed a few weeks or months previously begins to complain of some of the symptoms mentioned, the possibility of metastasis to the para-aortic nodes should always be considered. To overlook this possibility may be to rob the patient of months or years of life, to throw away the slight chance of a permanent cure or at least to deprive the patient of the partial or complete relief from pain and other symptoms which might readily be obtained by proper roentgen therapy. Too often, unfortunately, the factors responsible for the symptoms are not recognized, and their significance is overlooked until physical deterioration has progressed beyond even temporary salvage.

Physical Signs of Retroperitoneal Metastasis of Tumors of the Testis.—When the para-aortic lymph nodes have been invaded by metastasis from a tumor of the testis, the physical signs at first may be as slight and vague as the symptoms. As the nodes enlarge, however, they gradually form a mass, the greater portion of which is on the same side as the primary growth in the testis. It usually is situated in the epigastric and the upper part of the umbilical region, and more than half of it is to the right or left of the median line, according to the testis primarily involved. In some cases the metastatic growth may extend downward into the iliac region on the same side; this occurs when the lower para-aortic and the common iliac nodes also have been invaded, but almost always this follows metastasis to the upper group of para-aortic nodes.

When a definite mass cannot be palpated, a sensation of deep abnormal resistance can usually be felt, and pressure on this resistance elicits tenderness, which is usually slight or moderate. When these

physical signs are associated with the symptoms previously described, metastasis to the retroperitoneal lymph nodes may be assumed as probable.

When the distinct sensation of a mass is obtained, the mass may be nodular or fairly smooth; this probably depends on how closely packed the enlarged nodes are. Rather firm, the mass as a rule is fixed and immovable, but sometimes a slight degree of mobility may be perceived. Regardless of its consistency or mobility, however, pressure on the mass can be counted on to elicit a slight degree of tenderness. When the mass is situated mainly in the epigastric and the upper umbilical region on the left side, it may extend into the left hypochondriac region and may easily lead one to mistake it for an enlarged spleen or kidney. Such an error is far from rare. When, on the contrary, the bulk of the mass lies to the right of the median line, it is frequently mistaken for an enlarged liver. Of course, metastasis to the liver may occur in a case of this kind, but this is usually a late manifestation. Moreover, metastasis to the liver is relatively uncommon; the lungs are much more likely to be invaded. Careful palpation and percussion, with the abdomen relaxed as much as possible, generally enable one to distinguish between retroperitoneal nodes enlarged by metastasis from a tumor and an enlarged spleen, kidney or liver, especially if the great frequency of metastasis to the para-aortic nodes is kept in mind.

Another physical sign which may sometimes be found is moderate tenderness to deep palpation in the lumbar portion of the back, on each side of the spine, in the ninth, tenth or eleventh intercostal space and sometimes below the ribs. In this connection it is perhaps significant that the tenderness elicited by pressure along the lower part of the thoracic portion and the lumbar portion of the spine impresses the patient as having the same quality as the tenderness obtained by deep palpation through the anterior abdominal wall.

Physical Signs of Retroperitoneal Metastasis from Tumors of the Ovary.—These are the same as the signs described in the foregoing section, but frequently they are so masked by other signs (and symptoms) produced by more or less extensive dissemination of malignant elements to the peritoneum and other structures anterior to the para-aortic nodes that it is often difficult or impossible to recognize retroperitoneal metastasis with any degree of assurance. In some cases, nevertheless, the symptoms and physical signs may strongly suggest the possibility, and it is important to bear it in mind because if the pain is due largely or wholly to retroperitoneal metastasis, a considerable measure of relief may be afforded by roentgen treatment; this is possible, however, only when treatment is directed to the structures responsible for the pain. Indiscriminate irradiation of the abdomen, hip or lower extremity is not likely to have much, if any, favorable effect.

In many cases, unfortunately, a malignant tumor of the ovary has the character of cystadenoma or adenocarcinoma, a prominent complication of which is ascites, and this often makes palpation of the abdomen unsatisfactory. In other cases the bowel may be so distended with gas that all other physical signs are partly or completely obliterated.

LYMPHOBLASTOMA (HODGKIN'S DISEASE OR LYMPHOSARCOMA)

Important as metastasis to the para-aortic nodes or to both the para-aortic and mesenteric nodes often is in the presence of tumor of the bladder, prostate gland, rectum, uterus, testis or ovary, involvement of these nodes is still more important in Hodgkin's disease or lymphosarcoma. It is generally taken for granted that this type of disease, or, rather, this variety of tumor,[3] always begins in the cervical nodes and thence gradually extends to other groups of nodes. This is far from true. In a considerable proportion of cases the malignant process first affects the retroperitoneal nodes and gradually spreads to the nodes in other regions. But even when the neoplastic process has its origin in the cervical or the mediastinal nodes it almost invariably reaches the retroperitoneal nodes sooner or later. The time required for this transfer of malignant elements from the cervical to the retroperitoneal nodes may vary from a few months to several years. In some cases in which the pathologic process has apparently started in the retroperitoneal nodes, slight or moderate symptoms have been present for a long time before the patient is impelled to seek relief. The onset of symptoms is usually insidious and gradual; pain often either is absent or is moderate, inconstant or interrupted by more or less prolonged remissions, so that many patients bear with their distress for months or

3. From a clinical standpoint, at least, so-called Hodgkin's disease, as well as lymphosarcoma, is undoubtedly a malignant process or a variety of a malignant process affecting the lymph nodes and sometimes all the lymphoid structures in the body. If, as Furth and his co-workers have shown, leukemia in animals is a form of malignant disease, there would seem to be little ground for excluding from the same category Hodgkin's disease and lymphosarcoma (Furth, J.: Studies on the Nature of the Agent Transmitting Leucosis of Fowls: III. Resistance to Desiccation, to Glycerin, to Freezing and Thawing; Survival at Ice Box and Incubator Temperatures, J. Exper. Med. **55**:495-504 [March] 1932; Transmission of Myeloid Leukemia in Mice, Proc. Soc. Exper. Biol. & Med. **31**:923-925 [May] 1934; Transmission of Myeloid Leukemia of Mice: Its Relation to Myeloma, J. Exper. Med. **61**:423-445 [March] 1935. Furth, J., and Miller, H. K.: Studies on the Nature of the Agent Transmitting Leucosis of Fowls: II. Filtration of Leucemic Plasma, ibid. **55**:479-493 [March] 1932. Furth, J.; Seibold, H. R., and Rathbone, R. R.: Experimental Studies on Lymphomatosis of Mice, Am. J. Cancer **19**:521-604 [Nov.] 1933. Furth, J., and Strumia, M.: Studies on Transmissible Lymphoid Leucemia of Mice, J. Exper. Med. **53**:715-731 [May] 1931).

years before seeking to know the cause and have it removed. Unfortunately, the frequency of primary or secondary involvement of the para-aortic or mesenteric nodes is so seldom realized that the factors responsible for the patient's symptoms frequently go unrecognized for a long time or are regarded as representing a merely functional disturbance.

A striking feature is the great variety of the symptoms, and this perhaps more than anything else accounts for the difficulty which those who have not examined and followed a large number of patients with the disease have in recognizing the character and the cause of the patient's difficulties. One patient may complain chiefly or wholly of impairment of vision, thickening of the lids or bulging of the periocular tissues; another may complain of pain in the right upper quadrant or the right lower quadrant of the abdomen and may already have undergone cholecystectomy or appendectomy, with only temporary relief; another patient's chief or only complaint may be of itching which, having been confined for a time to the lower or upper extremities, has gradually extended to the entire body and has become so severe that restful sleep has become impossible; the principal difficulty of another patient may be pain in the back, radiating to one or both lower extremities; another may have as his chief or only symptom an "afternoon fever," which may be continuous or may occur in intermittent waves; another may suffer mainly from pain in the "stomach" occurring from one-half to three hours after meals; the chief complaint of another may be a progressive and unaccountable loss of weight; another may complain only of amenorrhea. And yet all these patients may be suffering from Hodgkin's disease or lymphosarcoma affecting the retroperitoneal nodes only or involving these and groups of nodes in other regions as well.

By the great variation in the symptoms and by the protean complications which may develop during their course, Hodgkin's disease and lymphosarcoma can simulate many diseases. So true is this that, as experience accumulates, an increasing proportion of the puzzling conditions which baffle physicians prove to be lymphoblastoma, and in many such cases the malignant process has apparently originated in the retroperitoneal nodes.

Before considering the individual symptoms I should like to point out that the history, if carefully taken, may often be sufficient to indicate the character of the pathologic process or to raise a strong suspicion of it. Moreover, when both the history and the physical findings point to lymphoblastoma, an accurate diagnosis can be made in a large percentage of cases without benefit of biopsy. In some cases, indeed, reliance on the results of the microscopic examination of an excised lymph node

may lead one astray. Not only in the first node excised but sometimes in three different nodes successively removed from the same region or from different regions may the pathologist be unable to find anything but inflammatory changes. In such cases a pathologic report of "inflammatory changes" should be regarded as a negative finding and investigation should be continued as if biopsy had not been done; that is, when the history and physical findings point strongly to lymphoblastoma, a finding of "inflammatory changes" should be disregarded, and the clinician should rely on the clinical features and the physical findings.

Occasionally the most experienced pathologist may have difficulty in distinguishing between a highly malignant epithelial cell tumor and Hodgkin's disease or lymphosarcoma and may report "squamous cell epithelioma of grade 4 malignancy" or even "adenocarcinoma" when both the history and the distribution of the lymphadenopathy are inconsistent with such a diagnosis. Sometimes, of course, the history and the physical findings are not entirely conclusive, but when they are the pathologic interpretation should be discarded as probably misleading or at least should not be allowed to outweigh all other evidence. Too often, when the clinician receives the report of a pathologist, he stops thinking and allows his judgment to lapse. The clinical and physical features of a case may point more accurately to the correct diagnosis than the microscopic changes.

To attempt to distinguish between Hodgkin's disease and lymphosarcoma by clinical features alone is to attempt the impossible. In the average case the two conditions are identical not only in their clinical manifestations, but also in their response to treatment. Not a single symptom or physical sign can be taken as a clearly distinctive feature. Therefore, any attempt to make such a distinction on clinical grounds is only a guess. Even microscopic examination is not free from difficulties in this respect, if one is to judge by the frequent inability of different pathologists to agree in their interpretations of tissue changes as representing Hodgkin's disease or lymphosarcoma. For these reasons it is desirable to avoid a distinction surrounded by such difficulties and uncertainties and to group both conditions under the collective term "lymphoblastoma." Clinicians, at least, might well do so.

Symptoms.—A common feature of the symptoms occurring in cases in which the retroperitoneal nodes are primarily or secondarily affected by lymphoblastoma is that they often vary considerably in degree from time to time. Treatment of different kinds may be followed by partial or complete remission of symptoms. For example, after cholecystectomy or appendectomy performed on the unfounded assumption that the abdominal pain was due to cholecystitis or to appendicitis the pain may diminish greatly or disappear, and the general condition may improve

considerably for weeks or months, only to return later. Simple medical treatment may be followed by temporary improvement, and even without any treatment the symptoms may subside and may be slight or absent altogether for a time.

Usually the extent of the condition roughly parallels the stage of its evolution or the point in its course, but exceptions are not uncommon. Sometimes the lymphoblastoma may have invaded nearly all the lymph nodes in the body and the patient may appear to be near death; the nodes in different regions may have enlarged enormously and may be causing more or less pronounced symptoms of pressure. Yet careful treatment with roentgen rays may cause rapid and marked regression of the lymphadenopathic masses and corresponding improvement in the symptoms, and if the treatment is properly followed and the patient kept under close observation life may be prolonged for many months or even for several years.

An idea widely held is that persons suffering from Hodgkin's disease or lymphosarcoma cannot be expected to live more than two or three years. This is true in a considerable proportion of cases, but many patients may live five, ten, fifteen and even twenty or more years. The two main factors which influence survival are: (1) the relative acuteness or chronicity of the disease in the individual case and (2) the quality of the treatment. Of these two factors the first is much more important than the second.

Lymphadenopathy.—A common feature is that the size of the enlarged lymph nodes often varies considerably from time to time, irrespective of treatment. Many patients suffering from Hodgkin's disease or lymphosarcoma are abnormally subject to infection of the respiratory tract. In the course of each infection of this kind or soon afterward the affected nodes tend to enlarge more or less rapidly for a time. Later the swelling may subside again, but it seldom disappears, although the patient may no longer be aware of its presence. In most cases of lymphoblastomatous invasion of the retroperitoneal nodes the patient is not aware of masses, lumps or tumors in the abdomen. Occasionally, however, the patient may have discovered a mass and may tell the physician that some weeks or months later the mass disappeared. Such a statement should never be accepted at face value. What it usually means is that the mass diminished until the patient could no longer feel it.

A true tumor of this or any other kind rarely disappears spontaneously. Sooner or later its further growth becomes manifest. While in most cases the tendency of the affected nodes is to increase in size until they attain considerable proportions, some cases are encountered in which the lymph nodes remain small throughout the course of the malignant process. The mere size of the nodes, therefore, cannot be taken as an indication of the stage of the process.

In relation to its importance, altogether too much attention is given to enlargement of the cervical, axillary and inguinal nodes. With a few exceptions, enlargement of these nodes never affects the general health of the patient. When general health has deteriorated, the lymphoblastomatous process has almost always invaded the nasopharynx, the tonsil or pharynx, the mediastinal nodes, the retroperitoneal nodes or the lymphoid tissue or lymph nodes in all four of the regions mentioned. When the nasopharynx, tonsil or pharynx is extensively involved, this may cause mechanical interference with respiration or deglutition. Similar difficulties may arise from enlargement of the mediastinal nodes. Occasionally, enlarged mediastinal nodes may cause circulatory embarrassment. In point of frequency as well as of relative importance, however, a deleterious influence on the general condition of the patient is much more likely to follow invasion of the retroperitoneal nodes than involvement of the mediastinal nodes or of the nasopharynx, tonsil or pharynx.

In general, involvement of the axillary or inguinal nodes, and especially of the latter, does not occur until the para-aortic nodes have been affected for some time. Therefore, except in the few cases in which the malignant process has originated in the inguinal nodes, enlargement of these nodes from lymphoblastomatous hyperplasia is usually associated with involvement of the retroperitoneal nodes and should cause one to suspect such involvement. Invasion of the axillary nodes does not have the same significance, but it may occur in association with lymphoblastoma affecting either the retroperitoneal or the mediastinal nodes. Rarely, the process may begin in the axillary nodes and may gradually spread from these to the nodes in other regions.

Secondary involvement of the retroperitoneal nodes in cases in which the lymphoblastomatous process has begun in some other region (cervical, mediastinal or inguinal) renders the prognosis more unfavorable. While the affected retroperitoneal nodes may retrogress and the related symptoms may abate or disappear after irradiation, prolonged control of the lymphadenopathy is more difficult to achieve than in the case of cervical, mediastinal or inguinal adenopathy. Moreover, roentgen or radium irradiation of the retroperitoneal nodes involves exposure of other comparatively sensitive structures, such as the small intestine and spleen, as well as of a large quantity of blood. A common result is more or less pronounced leukopenia, which, though usually temporary, may continue for weeks or months and may interfere with systematic treatment.

Loss of Strength.—Perhaps the most common symptom mentioned by patients suffering from lymphomatous invasion of the retroperitoneal nodes is a loss of strength, which is often expressed as "tiring easily,"

"loss of endurance" or "loss of pep." A man or woman who previously has been able to work steadily without undue fatigue finds it increasingly difficult to carry on as of old and complains of "being tired all the time," and this has nothing to do with the age of the patient or with his condition in other respects. A patient may not have any other symptoms for a long time and may not be aware that he is ill. Often this symptom is disregarded by the physician, who does not realize its significance or who, not finding evidence of any organic disturbance, may diagnose the patient's condition as neurasthenia.

When a patient known to be suffering from Hodgkin's disease or lymphosarcoma begins to complain of "feeling tired all the time," it may be taken almost for granted that the para-aortic nodes and perhaps also the mesenteric nodes have been invaded by the lymphoblastomatous process.

When a patient who is not known to be suffering from Hodgkin's disease or lymphosarcoma begins to complain of "feeling tired all the time," the possibility of lymphoblastoma should always be considered. If enlarged lymph nodes are found in other regions or if other symptoms of primary or secondary invasion of the para-aortic or mesenteric nodes are present the possibility becomes a probability or a certainty.

Loss of Weight.—When they first consult a physician, and often for a long time afterward, many patients affected by Hodgkin's disease or lymphosarcoma maintain their weight at or near the normal level. In many cases, therefore, loss of weight is not included among the patient's symptoms. Sometimes this is a significant feature in the differential diagnosis. For example, when symptoms pointing to an abdominal tumor have been present from one to five years, with little or only slight and gradual increase, and when the patient's weight and general condition are much better than would be expected the tumor is likely to be a lymphoblastoma rather than a carcinoma.

In other cases loss of weight, sometimes unaccountable, is a prominent symptom or the principal symptom. A patient may lose from 20 to 40 pounds (9 to 18 Kg.) in from two to six months, and it may be this alone which brings him to consult a physician. Such a complaint should always lead to a thorough investigation of the gastrointestinal tract and of the abdominal and pelvic structures generally. If evidence of an intrinsic, organic lesion as an adequate cause cannot be demonstrated and especially if one or more tumors extrinsic to the stomach, intestine or kidney are revealed by roentgenologic examination the possibility of primary or secondary lymphoblastoma of the retroperitoneal nodes should always be considered.

A curious circumstance is that the decrease in weight may occur in spite of a normal or ravenous appetite and a seemingly adequate intake

of food. Apparently the disturbance affects the absorption of foodstuffs or of essential vitamins by the small intestine.

Pain in the Abdomen.—In Hodgkin's disease and lymphosarcoma enlargement of the lymph nodes in regions other than the abdomen usually is not accompanied by pain. Sometimes the nodes may be slightly or moderately tender for a time, but this is seldom a prominent feature. Moreover, as time goes on, even the slight initial tenderness tends to diminish or disappear. It is precisely because of this common painlessness of the enlarged nodes that so many patients allow them to continue to enlarge for a long time before seeking medical attention. In fact, this absence of pain or tenderness often constitutes a valuable point of differentiation. Although not themselves tender, the lymph nodes may sometimes grow to such proportions as to cause more or less discomfort.

In general, this is as true of the retroperitoneal nodes as of the nodes in other regions. For many weeks or months, in many cases, the sensory disturbances are hardly sufficient to be designated as pain. However, as the malignant process continues and as the para-aortic nodes become increasingly large, varying degrees of discomfort or of actual pain manifest themselves. A noteworthy characteristic is a slow but more or less steady increase in discomfort or pain. In some cases this is interrupted at times by partial or complete relief for varying periods. At first the pain is often inconstant and slight, but as time goes on it gradually occurs more frequently until it becomes constant, and it also increases in severity. When the pain is constant, however, severe pain such as that which characterizes acute cholecystitis, nephrolithiasis or appendicitis is exceptional. In many cases the pain is described as a "dull ache" or "soreness."

Many patients complain of a heavy sensation in the epigastric region. Others complain of a sensation of "fulness in the stomach," especially after eating. Not infrequently a patient stresses his inability to eat a large or even an ordinary meal without discomfort, and some patients have learned that they can avoid distress by taking a small quantity of food at frequent intervals. Others voluntarily restrict themselves to milk and other liquid foods. This sense of undue fulness after eating appears to be a simple mechanical effect of the gradual increase in size of the para-aortic nodes or of both the para-aortic and mesenteric nodes and of the decreasing ability of the stomach to find room to expand with the amount of food taken.

Instead of a mere sense of heaviness or fulness, some patients complain of epigastric pain occurring from half an hour to three hours after meals and thus simulating the pain generally regarded as characterizing peptic ulcer. Gastroenterologists often speak or write of the pain of peptic ulcer as a "typical ulcer pain," but one cannot help

wondering if such an expression is warranted. Occasionally a patient with retroperitoneal lymphoblastoma may also have a gastric or duodenal ulcer, but another who does not have any ulcer may have the same kind of pain, and occasionally relief may follow the use of sodium bicarbonate just as is supposed to occur only in a patient with a gastric ulcer. Another point worth remembering is that in an occasional case a false roentgenologic appearance of duodenal ulcer may be produced by enlarged para-aortic lymph nodes in close anatomic relation to the pyloric end of the stomach, to the duodenum or to the head of the pancreas.

Occasionally pain in the epigastric region or in another part of the abdomen, such as the right lower quadrant, may become increasingly severe, and its character as well as the symptoms associated with it may suggest obstruction of some portion of the intestinal tract. In such a case an exploratory laparotomy may reveal obstruction of the duodenum, cecum or other part of the bowel by pressure from enlarged nodes adjacent to these structures or by actual infiltration of the intestine by the pathologic process affecting the nodes. Occasionally, also, pain in the epigastric region may be accompanied by nausea and vomiting, and roentgenologic examination of the stomach may disclose more or less extensive involvement of the organ. Careful exploration usually reveals more or less extensive involvement of the para-aortic or mesenteric nodes or both. Although it is possible for the intestine or stomach to be invaded independently by lymphoblastoma, it seems more likely that the intestinal or gastric involvement represents direct extension of the process from adjacent nodes. Lymphoblastoma sometimes has a distinct tendency to infiltrate adjacent tissues. This is seen when Hodgkin's disease or lymphosarcoma affecting the mediastinal nodes infiltrates the thoracic wall through the intercostal spaces and thus extends to the subcutaneous tissues or when it infiltrates the spinal canal.

In other cases the pain complained of is not in the epigastric region but is in the right iliac region or in the left side of the abdomen. Also, the pain may shift from one part of the abdomen to another, may vary greatly in duration and severity or may occur in waves strongly suggesting spastic contraction of the bowel, probably as a result of mechanical interference by enlarged para-aortic nodes or by enlarged nodes in the mesentery or both. Sometimes the pain is cramplike or colicky. When the pain is localized in the right iliac fossa or in the right upper quadrant of the abdomen it may be due to mechanical pressure on or infiltration of the right ureter by enlarged iliac nodes, sometimes causing partial or even complete obstruction of the ureter, with resulting hydronephrosis of the right kidney. The pain may also be due to

lymphoblastomatous infiltration of lymphoid tissue in the region of the appendix and cecum from adjacent right iliac nodes involved in the process; or it may be caused by pressure of enlarged iliac nodes against the ilium, and the pressure may be sufficient to cause erosion of the bone. When the pain is in the left lower quadrant it may be due to the first or third of the foregoing causes acting on that side.

Thus it may be seen that the character, site and severity of the pain may vary greatly, according to the nodes which happen to be the largest and the anatomic relation of the nodes to particular organs or structures.

Pain in the Back.—A rather common symptom of retroperitoneal lymphoblastoma is pain in the back. Some patients never have it, but many others suffer from it sooner or later, and in some cases it is the chief or only presenting symptom. Usually the pain is a dull ache and affects the lumbar region, but sometimes it extends to the lower part of the thoracic region or more often to the sacral region. In the beginning the pain is usually slight and may be described as a sort of "tired feeling" in the back. Inconstant at first, it gradually occurs more and more frequently and finally becomes practically constant; at the same time it increases in severity. Most patients describe it as a steady dull ache, which becomes severe or excruciating only when some of the spinal or pelvic bones become eroded by direct pressure or are invaded through the blood stream. In most cases it is worse at night than during the day. The pain may be entirely unilateral for some time but may later affect both sides. Even then it is usually more pronounced on one side, as a rule on the side on which it first developed; this is commonly the left side, although pain on the right side is almost as common.

Important features of this pain are its slow, gradual increase as the weeks and months roll by and its tendency to be projected to the corresponding hip and later down the corresponding lower extremity as far as the knee or the foot. Sometimes the patient also complains of numbness and tingling of the foot or of the foot and leg. Sometimes the pain around the knee and leg may be worse than the pain around the hip, or the latter may be absent altogether. When the backache affects both sides, just as it is usually more severe on the side affected, the pain in the corresponding hip and lower extremity is more severe than that on the opposite side.

This backache is undoubtedly caused by gradually increasing pressure of enlarging para-aortic lymph nodes on nerves which enter into the formation of the lumbosacral plexus. The circumstances all point to such a cause, and other reasons will be mentioned later.

Rarely, the pain in the back may appear with suddenness, and the circumstances may give an erroneous impression of traumatic origin. For example:

A woman of exceptional development and vigor, aged 36, who had always regarded herself as in the best of health, was driving her car. On coming to a stop and stepping out from the driver's seat, she was seized with a severe pain in the left side of the back. Instead of subsiding after a few days the pain had continued, increasing slowly but steadily week by week. Repeated examinations had failed to account for it. One and a half years after the day of onset she had been subjected to an unusually thorough examination, but a plausible cause for the pain had not been discovered. The possibility of enlarged retroperitoneal nodes had not been considered. As a palliative measure she had been fitted with a brace and instructed to return in three months. At the expiration of this interval she reported that the brace had provided considerable relief from the pain in the left side of the lumbar region but that the pain had "shifted" to the left hip, had been increasing steadily and now extended down the left lower extremity. She had considerable difficulty in walking. Ordinary and roentgenologic examinations again failed to furnish any clue to the cause of the patient's difficulty. Therefore, it was assumed that she must be suffering from sciatica, and she was referred for roentgen treatment.

The excellent general condition of the patient, the long duration of the pain and its gradual increase in extent and severity, the fact that the pain affected the lumbar region and was projected to the corresponding lower extremity and the fact that no other adequate cause could be found led me to suspect retroperitoneal lymphoblastoma. Physical signs of some kind of retroperitoneal adenopathy having been found,[4] roentgen treatment was planned on the assumption that if the pain was due to lymphoblastoma affecting the para-aortic lymph nodes it would be relieved largely or wholly within two to three weeks.

When the patient returned four weeks later the pain had almost disappeared. She was then given a second course of similar treatment and up to the time of this report has been entirely free from pain in the back or in the left lower extremity. Since then, however, lymph nodes in the neck and axilla have enlarged and have thus furnished clinical corroboration of the diagnosis of lymphoblastoma. In time other evidence of the process will doubtless appear.

This is the only case observed by me in which the backache seemed to develop suddenly. How can this seeming suddenness be accounted for? As the para-aortic nodes increase in size they adjust themselves to the surrounding tissues and to spaces between adjacent structures. When the available space is exhausted, however, the continued hyperplastic enlargement of the nodes begins to exert pressure on the bowel or stomach, on the nerves of the lumbosacral plexus or on other structures. In the case cited, anatomic adaptation had probably been taking place for a long time and had about reached its limit. In getting out of her car the patient had probably twisted herself in such a way as to crowd the enlarged retroperitoneal nodes beyond their limit of physiologic endurance, and pain had resulted.

4. These physical signs will be described later.

Occasionally a case is encountered in which the pain in the back, instead of being a dull ache, becomes severe or excruciating. This usually indicates erosion of spinal (lumbar) or pelvic bones by pressure of enlarging para-aortic or iliac nodes. Rarely, the pain in the lumbar region may remain dull while the pain radiating down one of the lower extremities gradually becomes so severe that the patient may be unable to tolerate even the weight of a sheet over the feet. Such excruciating pain indicates not mere pressure irritation on some branch or branches of the lumbosacral plexus but actual infiltration of the nerve or nerves. If this infiltration has not been present too long and if the affected nerves have not been injured beyond repair the pain can be relieved within one or two weeks by roentgen treatment. To direct the treatment to any part of the extremity itself is a waste of time, because the neural injury is usually not in the extremity but in the lumbar region. Treatment should be directed to the lumbar region and sometimes also to the lower part of the thoracic region in order to include all the nerve branches that go to form the plexus.

Because roentgenograms of the spine may disclose more or less pronounced evidence of chronic arthritis it is sometimes taken for granted that this condition is responsible for the backache; the patient may be given prolonged medicinal treatment or physical therapy, and tonsils, teeth, appendix or gallbladder may be sacrificed in a vain attempt to relieve the pain and remove its supposed causes. In spite of these measures, however, the pain continues with or without interruption. The slow but steady increase in pain, the presence of other symptoms pointing toward lymphoblastoma and especially the presence of lymphadenopathy in other regions should make one pause before assuming that the pain is due to arthritis. Occasionally, chronic arthritis in one or several parts of the body may be associated with lymphoblastoma. Hasty conclusions, therefore, are unwise. To assume that backache, with or without extension of the pain to the hips or lower extremities, is related to chronic alterations of the vertebral articulations revealed by roentgenography may result in injustice to the patient by robbing him of the chance of relief which in the case of lymphoblastoma might follow proper irradiation within a few days and sometimes within twenty-four hours. Chronic arthritis also may respond favorably to irradiation, but the response is much slower, and repeated treatment may be necessary to cause the pain to disappear.

In certain cases lymphoblastoma has a tendency to infiltrate tissues outside the lymph nodes, and this infiltration may become rather extensive. Thus, an entire breast or a breast and the superficial tissues of the corresponding half of the thorax may become densely infiltrated. Lymphoblastoma affecting the mediastinal nodes may infiltrate one or more intercostal spaces and may form a mass over the sternum; this

probably represents extension of the process along the lymphatic channels that accompany branches of the internal mammary vessels and may not be infiltration in the sense here referred to. Lymphoblastoma of the retroperitoneal nodes, however, may infiltrate the tissues of the back; this irregular and diffuse infiltration may extend to the spine and may even penetrate the spinal canal, involving the dura and cord and giving rise to various sensory and motor disturbances, which may be mistaken as indications of a primary tumor of the spinal cord.

Bloating and Belching.—Many patients include among their complaints a more or less pronounced tendency toward abdominal distention with gas, with or without a corresponding tendency to belch. Not infrequently, indeed, bloating, belching and a vague sense of epigastric discomfort may be the only symptoms noticed by the patient for several months and sometimes for several years. He may have consulted one or more physicians, who, not being aware that lymphoblastoma sometimes begins in the retroperitoneal nodes or disregarding the possible relationship of enlargement of nodes in other regions, may have treated the patient for achlorhydria, for peptic ulcer or for cholecystitis. Sometimes, because an obvious organic lesion is not found, the patient is branded as "neurasthenic," thenceforth to be shunned as a medical bore; or he is treated by "psychotherapy," or, more bluntly, by being given a "talking to" as if he were a malingerer.

When pronounced, distention and belching are greatest some time after eating, and they may be accompanied by soreness or actual pain. Some patients seek relief by taking sodium bicarbonate or by modifying their diet in various ways from the elimination of meats to the adoption of a diet exclusively of milk, but the degree of relief obtained varies greatly. Other patients mention bloating and belching after meals, without any pain or with only a sense of abdominal discomfort or of weight in the "stomach," by which the average person means the epigastric region or the abdomen in general.

These disturbances appear to result from some degree of mechanical interference by enlarged para-aortic or mesenteric nodes to the passage of gas from the loop of the duodenum into the jejunum; the main point of obstruction of gas, however, may be somewhat lower. Sometimes, with marked involvement of most of the para-aortic and iliac nodes, interference with the passage of gas may affect the colon as well as the small intestine, and abdominal distention, frequently accompanied by spastic pain, may be a prominent feature.

Nausea and Vomiting.—Less common than the aforementioned symptoms, nausea, alone or associated with vomiting, occurs often enough to deserve attention. At first slight, infrequent and irregular in their occurence, nausea and vomiting gradually tend to occur more

frequently; this, however, varies a great deal. Some patients have nausea without vomiting. In some cases nausea and vomiting never become a regular or prominent feature, whereas in others the time comes when, especially if the patient eats more than a small quantity of food, little can be retained, and weight is lost rapidly. The character of the food may be a definite factor; some patients report that they vomit only when they eat heavy or greasy foods. In certain extreme cases, however, nausea and vomiting may recur regularly after every meal, although some patients have learned by themselves that they can diminish the tendency by eating only liquid foods or by taking food in small quantities at short intervals. In most cases in which nausea and vomiting occur they are associated with a sense of weight, heaviness or pain in the epigastric region, with bloating and belching or with all these symptoms combined.

Fever.—At the outset, for a long time after it or throughout the course of their illness, most patients afflicted with Hodgkin's disease or lymphosarcoma do not have fever. It would be more accurate to say that they are not aware of fever. A certain proportion of patients do have fever, and it is probable that if the temperature of all patients should be taken regularly the proportion of febrile patients would be larger than it appears to be. Inasmuch as the fever in many cases is slight, many patients whose temperature rises above normal every day or almost every day are not aware of the rise until the fever is discovered by a physician. Often a patient's statement that he does not have any fever is accepted without verification.

Another point worthy of note is that if the distinction between Hodgkin's disease and lymphosarcoma which heretofore has been made and still is being made by pathologists is accepted, the fact remains that patients suffering from one condition or the other may have fever at some stage in the process, and the type of fever cannot be taken as an indication of the variety of lymphoblastoma. Patients with lymphosarcoma may have precisely the same kind of fever as patients with Hodgkin's disease.

Fever occurs almost always in the afternoon; the temperature in the morning is usually normal or subnormal. In some cases the fever is continuous, that is, it recurs daily for long periods, although it may be punctuated by occasional and irregular interruptions. As time goes on the fever gradually tends to increase, but this feature varies considerably in different cases. As the fever continues, the temperature in the afternoon tends to rise higher and higher; after a time the temperature in the morning also may be abnormal.

In other cases the fever occurs in waves, bouts or "attacks" which may last from one to several weeks, with a roughly similar interval

between them. During the first few days of each bout the afternoon fever is slight. Then the temperature increases slowly day by day to a maximum which in different patients may vary between 101 and 104 or 105 F. During the early stages of the malignant process the maximum temperature attained is rather low, but as the condition progresses the maximum during the successive bouts tends to rise. This is the type of fever to which the name "Pel-Ebstein" has been attached. When the malignant process is relatively acute,[5] the fever in successive bouts increases more rapidly than it does when the condition is chronic and continues for several years. As a rule, the Pel-Ebstein type of fever is more common in cases of relatively acute lymphoblastoma than when the lymphoblastomatous process is decidedly chronic, but exceptions are not rare.

An important point is that in either Hodgkin's disease or lymphosarcoma fever of the Pel-Ebstein or of the continuous variety indicates lymphoblastomatous invasion of the retroperitoneal or of the mediastinal nodes (usually the former). Moreover, this indication is so definite that it may be relied on even when enlarged abdominal nodes cannot be palpated. Why lymphoblastoma affecting the para-aortic or mesenteric nodes should cause fever and the same condition confined to the cervical nodes should not cause fever remains a puzzle. Nevertheless, the validity of this indication cannot be denied.

The reader will naturally ask on what grounds such a conclusion can be drawn. For years I have observed that when patients with Hodgkin's disease or lymphosarcoma have fever roentgen treatment directed exclusively to the abdomen through bilateral anterior and posterior fields causes the fever to abate or to disappear, whereas treatment directed to other regions but not to the abdomen causes the irradiated regional nodes to diminish in size but does not usually influence the fever. In a few cases, in which clear evidence of invasion of the mediastinal nodes was present but clinical evidence of invasion of the retroperitoneal nodes was uncertain, roentgen treatment directed to the mediastinum through bilateral anterior and posterior fields, with the four beams of rays converging on the mediastinal structures, was followed by reduction in the fever. However, the fields of irradiation were so large that they necessarily included some of the structures below the diaphragm, and this may have accounted for the lowering of temperature. It is for this reason that in the preceding paragraph the mediastinal nodes were included as a possibly associated, but doubtful, factor in this indication.

5. It is never as acute as some of the infectious fevers. In the form here called "relatively acute" the course of the condition from onset to death may extend over a period varying between six months and two years. In the chronic form the process may continue from three to twenty-five years or longer.

Further circumstantial evidence of the relation between fever and lymphoblastomatous invasion of the retroperitoneal nodes is to be found in an occasional case in which the patient's chief symptom is fever, possibly associated with loss of strength and sometimes loss of weight. In such a case the physical signs [6] of enlarged retroperitoneal nodes can usually be found, although sometimes they are vague and indefinite. When all examinations of the blood, urine and sputum for malaria, Malta fever, infection with Brucella abortus, infection of the urinary tract, tuberculosis, actinomycosis or other possible causes of fever yield only negative information, irradiation of the abdomen in the manner previously specified may cause the fever to diminish or disappear within from one to three weeks and may thus point to retroperitoneal lymphadenopathy as the source of the febrile disturbance. This therapeutic test with roentgen rays should not be overlooked in a case of this kind, because it often gives invaluable help in the presence of otherwise unaccountable fever. If the dose of roentgen rays given to each field is small (less than 300 roentgens measured in air) or if roentgen treatment is given through a single anterior and one posterior field, its influence on the fever may be only slight and transient—sometimes too slight to be recognized as an effect of irradiation. Even with larger doses (400 to 600 roentgens) given through multiple fields, the antipyretic effect must not be expected to last indefinitely; it may last from two or three weeks to two or more months, but after a variable period of reduced fever or complete apyrexia the fever usually returns. If a second course of roentgen irradiation is given three or four weeks after completion of the first course the antipyretic effect is more pronounced and continues longer than after a single course.

An important exception must be noted: When the malignant process has reached an advanced stage or has entered the terminal phase, the antipyretic influence of roentgen irradiation directed to the retroperitoneal nodes is less pronounced, the fever may not abate, or any lowering of temperature which may follow may be short lived. Usually the prognostic significance of the effect of irradiation is supported by other indications: either limited, transient regression of the irradiated lymph nodes, failure of the nodes to regress, increasing adenopathy in other regions, continued loss of strength and weight, increasing anemia or vice versa.

Many authors who have written on roentgen or radium therapy for Hodgkin's disease or lymphosarcoma have reported observing after irradiation of the neck or the mediastinum an increase in fever which the patient already had or an onset of fever in a patient who was not known to have had it previously, and they have regarded this fever as a phase of the reaction to roentgen rays or to radium. I have never

6. These signs will be described later.

had such an experience, although I have been watching for it for many years. The onset of fever or its increase in such a case almost certainly represents active invasion of the retroperitoneal nodes by the lymphoblastomatous process or increased activity of the same condition already established in these nodes. That extension of the process to the para-aortic or mesenteric nodes from some other group of nodes may follow irradiation of the latter is conceivable, but there is no good evidence to support the assumption that this is a direct effect of exposure to the rays. It seems much more likely that fever had been present previously but the patient himself had not been aware of it, or that the patient, having the Pel-Ebstein type of fever, did not have any fever immediately before the treatment but showed a rise in temperature during or soon after the irradiation; or that the systemic (gastrointestinal) reaction caused by irradition may indirectly have caused an increased activity in retroperitoneal nodes already affected by lymphoblastoma and may thus have been a factor in the onset of fever.

It must not be inferred that every unexplained fever is due to lymphoblastoma in the retroperitoneal nodes, but fever arising in a patient who is known to have Hodgkin's disease or lymphosarcoma points to invasion of the para-aortic or mesenteric nodes or both, whether enlarged nodes in the abdomen can or cannot be felt. In a patient with enlarged nodes in other regions suggesting the possibility of lymphoblastoma, the presence of fever, when it cannot be attributed to some infection, strengthens the possibility of lymphoblastoma and indicates the probable extension of the process to the retroperitoneal nodes. In a patient with lymphadenopathy in other regions, fever which cannot be traced to some infection may be due to lymphoblastoma affecting the retroperitoneal nodes and, if so, should abate or disappear for a time after irradiation unless the malignant process has reached an advanced stage.

Pruritus and Cutaneous Lesions.—Occurring in about the same proportion of cases as fever, pruritus may be the first or the only symptom noticed by the patient, or it may not develop until Hodgkin's disease or lymphosarcoma has been established for months or years. This does not imply that itching is to be expected only by a patient with fever; in fact, these two symptoms do not appear to be related, although in some cases they may both be present. As a rule the itching begins in one part of the body, such as the lower or upper extremities, and gradually extends to other parts. In some cases the face, the entire head or some other part of the body may be spared, while in others practically every inch of the body is affected. At first the pruritus is moderate, but gradually it becomes more and more severe until the patient spends much time and energy in scratching and finds it difficult

or impossible to sleep. Often the skin of the entire body is covered with scratch marks. Although the severity of the pruritus may vary considerably at different times, intense itching may continue for long periods.

Even when the patient is afflicted by intense pruritus, cutaneous lesions other than linear excoriations may be wholly absent. Sometimes, on the other hand, the itching is accompanied by macular, maculopapular or papular lesions which at first may be discrete and regional in their distribution but which, as they extend and increase, may gradually coalesce to form irregular patches. Exceptionally the skin may become diffusely infiltrated. This form also may have a regional or general distribution. Sometimes this infiltrative thickening of the skin is irregular; sometimes it is remarkably uniform. Still more rarely a case may be encountered in which the external appearance of the skin is entirely normal, the infiltration affecting only the deep layers of the skin and the subcutaneous tissues; this form of lesion is usually limited to one region, such as an upper extremity, but in time it may also affect the corresponding extremity on the opposite side without involving the skin or subcutaneous tissues of intervening regions.

When lesions of the skin are not present, those who are not familiar with the many vagaries of lymphoblastoma often fail to recognize the underlying cause of the pruritus because the relation between the two is not realized. When the pruritus is accompanied by circumscribed lesions or by a more or less general eruption, the condition is often mistaken for eczema, eczematoid dermatitis, scabies, psoriasis, urticaria, shingles or even impetigo.

Not every cutaneous eruption arising in a patient with Hodgkin's disease or lymphosarcoma is related to the malignant process. There is no reason why a patient afflicted with lymphoblastoma may not also have ordinary eczema, dermatitis or psoriasis, or why a patient with some form of dermatitis, scabies or psoriasis may not also become affected with lymphoblastoma. Hasty assumptions should by all means be avoided. Even when the cutaneous disturbance is definitely related to underlying lymphoblastoma it may respond to ordinary dermatologic treatment, but the degree of improvement is seldom great and the improvement is seldom lasting. When clear evidence of lymphoblastoma is provided by enlarged nodes which microscopically reveal the presence of Hodgkin's disease or lymphosarcoma or when numerous enlarged nodes in different regions suggest the probability of a lymphoid disorder of this kind, the association of local or general pruritus, with or without lesions in the skin, should always make one think of lymphoblastoma as a possible cause.

Just as, for reasons still unknown, fever is related to and is a sign of lymphoblastomatous invasion of the retroperitoneal nodes, so also pruritus and the cutaneous lesions with which it may be associated constitute another sign that the malignant process has extended to the para-aortic nodes or to these and to the mesenteric nodes as well. The same observation which has been mentioned in connection with fever applies also to pruritus. Roentgen irradiation directed to regions of the body other than the abdomen,[7] with the possible exception of the mediastinal nodes, does not influence the itching or the cutaneous lesions; but irradiation directed to the abdomen through large bilateral fields on both the anterior and posterior aspects causes the itching and the lesions to diminish or disappear. Moreover, the rate at which these manifestations subside or vanish corresponds to the rate at which lymph nodes affected by lymphoblastoma are known to be influenced by roentgen rays. As has been indicated, it is possible that lymphoblastoma in the mediastinal nodes also may play a part in the toxic cutaneous manifestations. Sometimes irradiation directed to the mediastinum may be followed by improvement in the condition of the skin, but even when the enlarged nodes decrease greatly in size the improvement which may follow mediastinal irradiation is slight as compared with the influence of roentgen rays on the retroperitoneal nodes. Inasmuch as when the mediastinal structures are irradiated the fields exposed usually are large enough to include some of the structures in the upper part of the abdomen, it is possible that the effect on the pruritus and on the cutaneous lesions may result from the action of the rays on retroperitoneal nodes included in the fields of irradiation rather than on the nodes in the mediastinum.

Increased Pigmentation of the Skin.—In a small percentage of cases the color of the skin becomes darker than normal. This change may be slight and the skin may have a muddy or dusky appearance, or the increase in pigment may gradually become so great that the skin becomes light dirty bronze. In the axilla and groin the skin is still darker. Sometimes the pigmentation suggests Addison's disease, but the other stigmas usually are absent. Whether this abnormal increase in pigment is due to lymphoblastomatous invasion of the adrenal glands or of aberrant chromaffin tissue is not yet clear. At any rate, it is certainly caused by a disturbance in the formation or distribution of pigment. Whatever may be the mechanism involved in this change, increased pigmentation of the skin is another indication that the lymphoblastoma has invaded the retroperitoneal lymph nodes. Unless the malignant process has reached an advanced stage, well planned roentgen irradiation can be counted on to improve the patient's condition. As the affected lymph

7. When the entire abdomen is shielded from exposure.

nodes in different parts of the body diminish in size, the pigmentation gradually decreases. After several courses of treatment the skin may have resumed an almost normal color, but in most cases this ideal result is never achieved, and some degree of abnormal pigmentation persists indefinitely.

Constipation.—Many patients with Hodgkin's disease or lymphosarcoma complain of constipation, the degree of which is often proportional to the degree of other symptoms, such as bloating and belching, pain in the abdomen or in the lumbar portion of the back, fever and itching. Constipation is so prevalent in otherwise normal persons that too much significance must not be attached to it. Nevertheless, the onset of constipation in a person who has never or seldom been troubled with it and its steady increase, sometimes to such a point that daily enemas become insufficient to clear the colon, should lead one to relate it to enlargement of the para-aortic or mesenteric nodes and to consequent mechanical interference with the motor function of the bowel, especially when other concurrent indications of retroperitoneal adenopathy are present. Absolute proof of such a relation cannot be submitted, but strong circumstantial evidence is available. Often the constipation diminishes or disappears after roentgen irradiation of the abdomen has caused the enlarged retroperitoneal nodes to retrogress. Later, as these nodes enlarge again, the constipation returns. A succession of similar cycles can sometimes be observed.

Diarrhea.—Diarrhea is not a common symptom but does occur in certain cases. Sometimes it takes the form of short bouts, the duration of which may vary from two or three days to one or two weeks, the bouts recurring at varying intervals. Occasionally the diarrhea may continue indefinitely, although it may vary considerably in degree from time to time. Generally slight at the beginning, it tends to increase gradually. The patient loses weight and strength, sometimes at an alarming rate. Often there is a ravenous appetite, and the quantity of food eaten may be greater than normal. Nevertheless, weight and strength continue to decrease slowly or rapidly according to the severity of the diarrhea. The patient may lose from 10 to 40 pounds (4.5 to 18 Kg.) in from one to six months, and ordinary efforts at treatment may be of little or no avail; any improvement obtained usually proves only temporary. Suitable exposure of the abdomen to roentgen rays, on the contrary, is often followed by striking improvement. Unfortunately, the favorable effect of a single course of treatment is only temporary; the duration of this effect varies considerably in different patients. Repeated irradiation of the abdomen may arrest the diarrhea permanently, but the evolution of the malignant process may not be otherwise influenced. In all probability, diarrhea with or without

tarry stools indicates infiltration of the bowel (solitary follicles and Peyer's patches) by the lymphoblastomatous process.

Edema.—Although relatively uncommon, edema occurs often enough to deserve attention. If lymphoblastoma is considered as a whole and not only as it affects the retroperitoneal, iliac and pelvic nodes, edema of the lower extremities occurs somewhat more frequently than edema of the upper extremities, but the difference is not great. In the lower extremities it usually affects first the feet and ankles and may then gradually extend to the legs; only in exceptional cases is the edema sufficiently pronounced to affect an entire lower extremity, and it is still more rare for the edema to affect the scrotum and the lower part of the abdominal wall. Bilateral edema usually is greater on one side than on the other, and nearly always this is the side on which the edema first appeared.

When a cardiac or renal disturbance cannot be found to explain it, edema of one or both lower extremities or of some portion of them indicates not blockage of the femoral vessels by enlarged inguinal nodes but interference with circulation through the external iliac vessels by enlarged external iliac nodes. When edema has extended also to the lower part of the trunk, notably to the scrotum, penis, pubic region and lower portion of the abdomen, it indicates interference with circulation through the common iliac vessels by enlarged common iliac nodes. The degree and extent of the edema may vary according to the degree of interference by the nodes; as a rule this is roughly proportional to their size, but not always. The anatomic relation of the nodes to the vessels appears to be as important as their size. Interference with circulation below the bifurcation of the common iliac vessels is generally compensated by increased circulation through collateral vessels. In cases of edema of the lower extremities, deep palpation in the iliac regions on one or both sides usually reveals enlarged nodes, which may be distinctly felt as such, or an abnormal diffuse resistance without perceptible nodulation. In either case pressure on the nodes or on the resistance elicits slight or moderate tenderness. Of course, when the abdominal wall is thick with fat or exceptionally muscular or when the abdomen is distended with gas or fluid, these physical signs may be difficult or impossible to make out. Exposure to roentgen rays causes the edema to diminish or disappear more or less rapidly as the nodes retrogress. The only exceptions are seen in cases in which the malignant process has reached an advanced stage or in which frequently repeated exposures to excessive quantitative doses of rays have caused the nodes to become resistant to irradiation.

Ascites.—In some cases of Hodgkin's disease or lymphosarcoma affecting the abdominal nodes ascites may be present when the patient

first consults a physician. This does not mean that fluid in the peritoneal cavity is an early sign of lymphoblastomatous invasion of the abdominal nodes. Almost invariably a careful inquiry into antecedent events reveals that the patient has had various gastrointestinal or abdominal disturbances for weeks, months or years. These disturbances may have been vague or definite, and the patient may have sought medical advice previously, but the cause of the symptoms often has not been recognized or even suspected. The ascitic fluid may be clear serum, a mixture of serum and blood or chyle. When the fluid is serous, the ascites is due to interference with the portal circulation. When the fluid is serosanguineous, the previous factor is associated either with erosion and hemorrhagic extravasation along the intestinal tract or with modifications in the blood, causing it to seep through the vessels and tissues at points where these have been weakened by the pathologic process. When the fluid has the character of chyle, the portal vessels are not affected; the seepage of chyle is due to blockage of the mouth or the lower part of the thoracic duct by enlarged para-aortic nodes.

When lymphoblastoma involves the abdominal nodes primarily or secondarily it may be confined to the para-aortic nodes or to the para-aortic and mesenteric nodes for a long time, but sooner or later, the malignant process may extend to other groups of nodes; in extreme cases all the lymph nodes and other aggregations of lymphoid tissue, such as the intestinal follicles, Peyer's patches and the lymphoid tissue in the appendix and in the vicinity of the ileocecal valve, may become infiltrated. Sometimes the para-aortic, mesenteric and other nodes become so large or are so situated with reference to the portal vessels that they impede the circulation through these vessels. Sometimes the para-aortic nodes in the vicinity of the celiac axis become so large that they block the receptaculum chyli sufficiently to cause chyle to seep into the peritoneal cavity. In other cases the close anatomic relations between these nodes and the stomach or duodenum may lead to lymphoblastomatous infiltration of these structures, and seepage of blood or frank hemorrhage may result.

Jaundice.—When first examined many patients appear pale, and some have a pasty or sallow complexion. Not infrequently the skin and the ocular conjunctiva have a faintly yellowish tint, but this is seldom sufficient to be designated as jaundice. True jaundice of any degree is comparatively rare. That it can occur, however, is undeniable, and its presence indicates one of three possible causes: when slight it indicates (1) impedence of the flow of bile through the common bile duct from infiltration of the duct by enlarged lymph nodes or (2) changes in the blood, or both; when marked, it indicates (3) lymphoblastomatous infiltration of the liver. The last usually represents an advanced stage of the disease.

When anemia or involvement of the liver is not present, the pale, pasty or sallow appearance of the skin often gives way to a more healthy appearance when roentgen therapy causes the lymphadenopathy to retrogress and the patient's general condition to improve. This improved appearance may last only a short time, or it may continue for months or years, especially in the chronic form of the disease. True jaundice, on the contrary, is seldom influenced favorably for a long time, if at all, probably because its presence denotes advanced lymphoblastoma.

Urinary Disturbances.—Occasionally a patient may include among his symptoms an increased frequency of urination and sometimes hematuria. Under these circumstances the possibility of hydronephrosis or pyelonephrosis must be kept in mind. The condition may be due to pressure on the ureter by enlarged iliac or para-aortic nodes or to infiltration of the ureter or of the renal pelvis by direct extension of lymphoblastoma from adjacent para-aortic nodes. Rarely, the kidney itself may be affected by the same process or through the blood stream.

Symptoms Related to Pelvic Organs.—Besides the many symptoms resulting from lymphoblastomatous invasion of the para-aortic, mesenteric and iliac nodes, some patients complain of increasing frequency of urination. In males this may be due to coincident hypertrophy of the prostate gland or to prostatitis, and in females it may be related to an associated fibromyomatous condition of the uterus. Frequently, however, conditions such as those mentioned cannot be found. Some patients complain of a dull soreness in the pelvis, some mention the passage of increasing quantities of mucus with the feces, but the majority of patients do not have any symptoms to suggest pelvic involvement. In a few cases one of the patient's symptoms, and sometimes the chief or only complaint, is irregular menstruation or complete amenorrhea. Pelvic disturbances may be a direct result of lymphoblastomatous invasion of pelvic lymph nodes or an indirect result of invasion of the para-aortic nodes; sometimes they may be the patient's first indication that all is not well, but usually they develop later in the course of the disease. As a rule they are associated with other symptoms, such as lymphadenopathy, loss of weight, lumbar backache, fever or pruritus. Amenorrhea as one of the chief symptoms is uncommon and usually occurs in young women. Amenorrhea or irregular menstruation arising after other manifestations of lymphoblastoma have been present for some time is much more common.

By itself, not one of the symptoms described can be taken as pathognomonic of abdominal lymphoblastoma, but when the history points to a gradual increase in any of them, with or without variations or remissions, the possibility of lymphoblastoma affecting the retroperitoneal

nodes should be considered. When enlarged nodes in other regions are present and when one or several of the symptoms mentioned develop and progress more or less steadily, the possibility of abdominal lymphoblastoma becomes a probability. When the patient is known to have Hodgkin's disease or lymphosarcoma, the appearance of one or more of the symptoms described increases the probability of invasion of the retroperitoneal nodes to a greater or less extent, according to the definiteness and degree of the symptoms.

Physical Signs.—Slight primary or secondary involvement of the para-aortic lymph nodes by Hodgkin's disease or lymphosarcoma probably does not produce physical signs that can be recognized by the methods of examination now available; also it probably does not cause any symptoms. But when the process has evolved and the size of the nodes has increased sufficiently to cause functional disturbances, certain physical signs usually are present; they may be so slight as to be difficult to perceive, or they may be so marked that it is hard to understand how any one could fail to recognize them. That they often go unrecognized or that they are often mistaken for something else is a matter of frequent observation. One reason is that the frequency of abdominal lymphoblastoma is not realized, and another reason is that few physicians have learned how to examine the abdomen for malignant invasion of the retroperitoneal nodes.

To examine the abdomen of a patient for metastasis to the retroperitoneal lymph nodes with some chance of obtaining maximum information, certain conditions must be fulfilled. The patient must be placed in a recumbent position with the head slightly flexed on the thorax. Still more important, the thighs should be flexed on the trunk and the upper extremities should be at rest along the trunk. The patient's breathing through the mouth may help to relax the anterior abdominal wall.

When the abdomen of a normal person is examined, unless the anterior abdominal wall is obese or exceptionally muscular or unless the abdomen is distended with fluid or gas, downward pressure yields a sensation of hollow organs containing air or gas, and the wall can be depressed until it comes in contact with the spine without any other adventitious resistance being encountered. Moreover, the only sensation experienced by the patient is that of the pressure exerted by the examiner's hand. Although this pressure may be more or less uncomfortable, there is no tenderness. When their attention is drawn to it, most patients can readily distinguish between actual tenderness and the discomfort caused by mere pressure, even when tenderness is slight.

When the para-aortic nodes are affected by lymphoblastoma and have attained a large size (fig. 4), they are sometimes readily felt as nodular masses in the epigastric or in the right or left hypochondriac region.

Sometimes palpable masses are scattered throughout the abdomen. In most cases of this kind the mass or masses are fixed and do not move with respiration, but in some they have a limited degree of mobility. Occasionally a case is encountered in which one or more tumors may be moved readily, as if connected by a pedicle. This is likely to mean that the movable node or nodes are related to the mesocolon or are situated in the peripheral portion of the mesentery of the small intestine. Certainly it would be difficult to understand how any of the para-aortic

Fig. 4.—Mass of enlarged para-aortic nodes in a case of lymphoblastoma. As may be seen, the mass extends from the celiac axis to slightly below the bifurcation of the abdominal aorta. In some cases the nodes are much larger than those shown.

nodes or of the nodes in the root of the mesentery could have more than a slight degree of mobility.

In lymphoblastoma the spleen or liver or both may be enlarged independently of the retroperitoneal nodes or as part of the pathologic process affecting these nodes. When the spleen is invaded it may enlarge slightly or moderately, but almost never does it assume the proportions

encountered in myeloid leukemia. When metastasis to the liver occurs, this organ also may enlarge slightly or moderately, but as a rule hepatic metastasis is a relatively late complication. To many physicians a mass in the left upper quadrant of the abdomen must represent the spleen or the left kidney, and a mass in the right upper quadrant must represent the liver or the right kidney. Usually there is little difficulty in distinguishing the spleen or the liver from enlarged retroperitoneal nodes provided the possible involvement of these nodes is kept in mind and the examination is arranged accordingly.

Another point not infrequently leads to misinterpretation: When the lower border of the liver can be felt below the costal margin, it is often assumed that the organ is abnormally large. The mere fact that the lower border of the liver extends below the costal margin does not constitute proof of enlargement; it proves only that the lower border of the organ is lower than normal. When retroperitoneal lymphoblastoma is followed closely and systematically, it is found that as the para-aortic nodes (and the mesenteric nodes also when they are involved) retrogress after roentgen irradiation the liver frequently returns to its normal position. Therefore, it seems most likely that at the time of the first examination the liver was not abnormally large but had gradually been crowded forward and downward as the size of the retroperitoneal nodes increased. The position of the para-aortic nodes on each side of the abdominal aorta, as well as in front of it and behind it, and the important group of these nodes in the region of the celiac axis (behind the stomach and in close relation to the pancreas) often brings them in close relation with the crura of the diaphragm. When the lymphoblastomatous process affects not only the para-aortic nodes but the mediastinal nodes also, and when all these nodes attain the considerable volume they sometimes do, all the structures situated in front of the nodes are gradually crowded more and more toward the front. This undoubtedly explains the abdominal discomfort, soreness or pain, the sense of heaviness or fulness in the epigastric region after eating, the inability of many patients to eat a full meal and also the forward and downward displacement of the liver. Even when the mediastinal nodes are not perceptibly affected, the involved para-aortic nodes may be so large as to displace the liver. To some extent the spleen also may be displaced downward by the enlarged para-aortic nodes.

In the majority of cases of lymphoblastoma affecting the retroperitoneal nodes primarily or secondarily, definite masses cannot be felt. This is why the average physician so often fails to recognize the physical signs of such involvement. Unless he can feel a mass or masses the size of a golf ball or baseball he concludes that a tumor is not present. In most cases of abdominal lymphoblastoma, masses of any size cannot

be palpated, probably because the para-aortic and mesenteric nodes are not large enough, because they are closely packed or because they are covered by other structures (intestine, omentum) to such an extent that individual nodes cannot be perceived. When pressure on the anterior abdominal wall is made, the examiner's hand feels in the upper half or the upper two thirds of the abdomen a deep resistance which is abnormal. This may be slight or marked; it may be more pronounced on one side than on the other, or it may be evenly distributed across the epigastric region and may extend into the right and left hypochondriac regions as well. When this deep resistance is greater on one side than on the other or when it appears to be confined to one side, it often extends longitudinally into the lumbar and sometimes also into the iliac region on the same side. In a large proportion of cases a considerable difference between the two sides is unmistakable. Many physicians recognize this resistance without realizing its significance; some ascribe it to muscular rigidity. And yet in most cases there is a clear difference between ordinary muscular rigidity and the deep resistance caused by enlarged retroperitoneal nodes. The former is immediately beneath the hand and is resilient or yielding, although this characteristic may be slight. The abnormal resistance due to malignant involvement of the retroperitoneal nodes is deeper and is not resilient. It may yield to pressure, but always one has the sensation of something solid. This sensation of solidity may vary considerably; sometimes the consistency is firm, and sometimes it is rather soft and boggy. In some cases a sense of vague nodulation can be perceived, while in others the deep resistance is diffuse.

When the deep resistance is marked and especially when it is diffuse and has a boggy or doughy character, lymphoblastomatous involvement of the mesenteric nodes also may be suspected. Inasmuch as the consistency of the enlarged nodes depends partly on the relative acuteness or chronicity of the malignant process and partly on its stage of evolution in the different patients, considerable variation is to be expected. Relatively speaking, the more acute the lymphoblastoma and the more rapid its evolution, the softer and the more boggy the lymph nodes tend to be. At necropsy in cases in which the deep resistance in the epigastric and umbilical regions was notably diffuse and boggy the mesentery has been observed to be so thoroughly infiltrated with closely packed hyperplastic lymph nodes that its thickness varied (fig. 5) between ½ inch and nearly 1 inch (1.3 and 2.5 cm.). Sometimes deep resistance in the epigastric or umbilical region may be so slight as to leave one in doubt. Deep palpation should then be made on each side of the spine and outward in the hypochondriac, lumbar and iliac regions.

The other important sign is tenderness. When a sensation of deep abnormal resistance is obtained, pressure on the resistant tissues or structures elicits a slight or moderate tenderness which is not normal.

The patient says, "That hurts," and winces or tries to draw away. The tenderness is seldom severe, but it is usually definite enough to leave no doubt. Until their attention has been drawn to it, some patients are inclined to attribute this tenderness to the pressure made by the examiner; but when their attention is directly attracted and pressure is made on another region for comparison, few patients have any difficulty in recognizing the difference. Even when deep resistance cannot be clearly perceived, slight or moderate tenderness on deep palpation should be regarded as abnormal. If the history suggests lymphoblastoma or if other clinical features of the condition are present, tenderness on deep palpation of the abdomen changes the possibility of invasion of the retroperitoneal nodes into a probability.

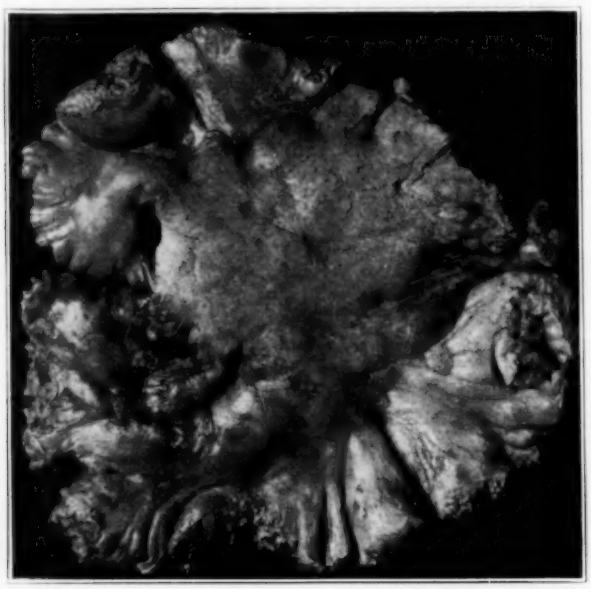

Fig. 5.—Massive infiltration of the mesenteric lymph nodes in a case of lymphoblastoma with extensive invasion of the abdominal lymph nodes. The hyperplastic nodes in the mesentery were so closely packed that the entire structure was diffusely and greatly thickened.

Physical Signs Related to Pelvic Disturbances.—In the majority of cases, when a patient afflicted with Hodgkin's disease or lymphosarcoma is subjected to rectal or vaginal examination, evidence of enlarged pelvic lymph nodes cannot be found. In a minority of cases moderately enlarged nodes may be found on the pelvic floor, and sometimes large masses in the pelvis may be discovered. When the patient is a woman, it is important to distinguish such a mass from a fibroid uterus, from an ovarian cyst or from pyosalpinx. As a rule, the history of the patient's

illness and other physical signs help to make this distinction, but one must remember that two or all three of these conditions may be coincidental in the same patient. When amenorrhea or irregular menstruation is present, evidence of pelvic adenopathy may be entirely lacking; these symptoms may be due to deterioration in the patient's general condition, usually resulting from involvement of the retroperitoneal nodes.

Occasionally, proctoscopic examination of the rectal and sigmoid portions of the colon may disclose extrinsic lesions, but even intrinsic lesions may be found, and these may be mistaken for carcinoma.

Uncommon or Rare Findings.—Auscultation along the median line of the abdomen may sometimes elicit an abnormal bruit the nature and cause of which may be puzzling. As the retroperitoneal nodes regress after roentgen irradiation of the abdomen this bruit diminishes or disappears, but it may return some weeks or months later. Blackford [8] reported such a case in 1928. The rate at which this bruit diminishes or disappears after roentgen irradiation corresponds to the rate at which the lymphoblastomatous retroperitoneal nodes are caused to retrogress by irradiation. It seems probable, therefore, that the abnormal bruit is due to crowding or interference with the normal expansion of the abdominal aorta by a ring of enlarged retroperitoneal nodes, which may even cause partial constriction of this vessel.

Roentgenologic Findings.—In a great majority of cases in which the para-aortic lymph nodes are affected by Hodgkin's disease or lymphosarcoma, roentgenologic examination of the gastrointestinal tract does not yield any evidence of abnormality. Sometimes, however, local abnormality of contour, otherwise known as a "filling defect," may be found in the stomach or in the small or large intestine. Usually the defect is not constant in outline and is caused by extrinsic pressure. Occasionally the defect in the outline of the gastric or intestinal lumen is permanent (intrinsic) and may lead the most practiced roentgenologist into regarding it as evidence of carcinoma. Even the surgeon who undertakes to operate in such a case may be deceived, and the real character of the lesion may not be realized until the pathologist has examined sections of excised tissue. When the stomach is involved, the natural question is whether or not the diseased part of the organ should be resected. Inasmuch as in most cases gastric involvement is probably secondary to antecedent disease affecting the upper para-aortic nodes immediately behind the stomach, it would seem wise, before undertaking to excise a part of the organ, carefully to explore the entire region for enlarged nodes, especially the tissues along the upper part of the abdom-

8. Blackford, L. M.: Tumor Compressing the Abdominal Aorta, Proc. Staff Meet., Mayo Clin. **3**:191-193 (June 27) 1928.

inal aorta. If the para-aortic nodes are involved, the advisability of gastric resection would seem at least doubtful.

Sometimes a permanent "filling defect" may be found in the cecum. This portion of the colon may be obstructed more or less by lymphoblastomatous infiltration, and intussusception may have occurred. An enterostomy may have to be performed to relieve the immediate difficulty, but the advisability of resecting a portion of the colon and perhaps also a portion of the small intestine would seem to depend on the presence or absence of lymphoblastoma in the para-aortic, mesenteric or common iliac nodes.

In some cases roentgenographic examination of the spine may reveal more or less pronounced arthritic changes; these changes may or may not be connected with the pain in the back, hips or lower extremities, and such a relation should never be assumed without careful consideration of all factors. Lymphoblastoma and chronic arthritis may each play a part, or the pain may be due to one or the other condition.

When a patient complains of increasingly severe backache, roentgenologic examination of the spinal and pelvic bones may occasionally disclose more or less extensive destruction of one or more of the lower dorsal or lumbar vertebrae or of a portion of the iliac bones. The question is whether such destruction has resulted from pressure and secondary infiltration by enlarging para-aortic or iliac nodes or whether disintegration of the affected bone or bones is secondary to involvement of the bone marrow. An absolute answer to this question cannot be given at present, but in many cases the presence of contiguous nodes which have been enlarging gradually for some time seems to indicate that pressure erosion is probably a more common factor than extension outward from intrinsic involvement of the bone marrow. Another point in favor of this view is that as the retroperitoneal or iliac nodes retrogress after roentgen irradiation, some degree of repair of the affected bones is frequently observed. This bit of circumstantial evidence, however, is not conclusive, because when the para-aortic or iliac nodes are irradiated the affected vertebral or iliac bones also are exposed to the rays. Unfortunately, such involvement of bone usually accompanies extensive and rather advanced disease.

Occasionally urographic examination may disclose dilatation of the ureter and of the pelvis of the corresponding kidney, but an experienced urologist seldom has any difficulty in recognizing the fact that these abnormal appearances are due to extrinsic pressure. Rarely, however, the pelvis of the kidney and sometimes the kidney itself may be infiltrated by lymphoblastoma. In such a case, symptoms, such as hematuria, and other clinical features usually point to the disturbance, but when enlarged lymph nodes in other regions cannot be found, a radiotherapeutic test may be required to solve the problem.

ACUTE SEGMENTAL APPENDICITIS

EXPERIMENTAL AND CLINICAL STUDIES

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In a previous communication [1] attention was called to a segmental type of appendicitis, characterized by a sharply demarcated lesion involving only a part of the organ. Further observations have revealed that not only does the single area of segmental involvement occur, but occasionally "skip" appendicitis, in which two or more areas of focal inflammation are separated by apparently normal appendical tissue. The gross features were particularly striking since they bore a close similarity to lesions seen elsewhere in the intestine.[2] The present study is concerned with the genesis of acute segmental appendicitis.

ANATOMIC CONSIDERATIONS

The experimental production of acute segmental appendicitis in the rabbit rests on two basic factors. The first is the peculiar segmental distribution of the appendical blood supply. The second is the striking similarity of the pathologic picture observed after vascular ligation in the rabbit to the pathologic process observed in man.

Certain embryologic and anatomic considerations are of interest in connection with the appendix and its blood supply. The organ may be regarded as a part of the general cecal pouch which has persisted in its early stage of development. Huntington [3] stated that "all the varieties of cecal apparatus met with in different species can be traced to one common primitive type from which they have all developed in accordance with varying conditions of alimentation." In herbivora, such as the rabbit and the horse, "whose food contains a relatively small amount

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From the Department of Laboratories and Research of the Bronx Hospital.

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1. Felsen, J.: The Pathological Appendix, Am. J. Roentgenol. **31**:340 (March) 1934.

2. Felsen, J.: Cases of Intestinal Ulceration with Special Reference to Amebic Dysentery, Am. J. Digest. Dis. & Nutrition **1**:297 (July) 1934.

3. Huntington, G. S.: The Cecum and Vermiform Appendix, Soc. Lying-In Hosp. Med. Rep., 1893-1894; cited by Kelly and Hurdon.[4]

of nutriment in proportion to bulk and requires a longer time to digest we find a most complicated and highly developed cecal apparatus." The appendix is proportionately larger than the human appendix. In carnivora, such as the cat family, "whose food is concentrated, easily and rapidly digested and contains little nonnutritive material, the cecum is reduced." The appendix is relatively smaller than that of man. Because of these factors the rabbit's appendix closely approximates in size that of man. We shall now attempt to point out the similarity in blood supply, for it is these two features which make the rabbit peculiarly suitable for the experimental work to be described.

In the 7 month human fetus the blood supply of the cecum and that of the appendix are separate except for some minor anastomoses at the junction of these organs. Kelly and Hurdon [4] stated that in man there is usually a single appendical artery which arises directly from the posterior ileocecal artery or from one of its branches and is carried in the free edge of the mesentery. This vessel supplies the entire appendix and sometimes a small part of the adjacent cecum in about one third of the cases. In the remainder it supplies only the distal four fifths of the appendix, accessory arteries supplying the proximal portion and anastomosing with cecal branches. From the main appendical vessel arise generally five secondary branches, which proceed direct to the appendix. Although Romanis and Mitchiner,[5] in common with other authors, have stated that the tip of the appendix often receives a poor blood supply because the mesentery stops somewhat short of it, Kelly and Hurdon observed no such deficiency. Each of the five secondary branches described divides near the mesenteric border of the appendix into two or more subdivisions. After penetrating the wall of the appendix these vessels form two main intramural networks, the serosal and the submucosal. The former sends some branches to the muscular coats. The latter penetrates the muscularis to reach the submucosa, whence most of the branches pass to the mucosa. There they form delicate filamentous networks which embrace the solitary acuminate lymph nodules and send branches into their substance. Other branches reach the crypts and the mucosa. We have been able to demonstrate the distribution of these vessels by means of transparencies, with and without previous injection.[6] It appears that the extreme paucity of anasto-

4. Kelly, H. A., and Hurdon, E.: The Vermiform Appendix and Its Diseases, Philadelphia, W. B. Saunders Company, 1905.

5. Romanis, W. H. C., and Mitchiner, P. H.: The Science and Practice of Surgery, ed. 6, London, J. & A. Churchill, Ltd., 1937, vol. 2.

6. Felsen, J.: Intestinal Illuminator: A Device for Detecting Intestinal Lesions in Postmortem Specimens by Reflected and Transmitted Light, J. Lab. & Clin. Med. **21**:923 (June) 1936.

motic branches within both the mesentery and the appendical wall justifies the practical consideration of the five branches of the main artery as terminal vessels. Previously described by Van Cott,[7] Brunn [8] and others, the subject was admirably presented in 1927 by Graham [9] and in 1932 by Seng.[10] By injecting an opaque substance into the vascular system of the appendix in human cadavers, the latter demonstrated that the submucosal and serosal vessels are connected only by capillaries and thus are really terminal arteries. Brunn went so far as to divide the appendix into from seven to fifteen segments, each with a restricted vascular supply, and described sharply segmental inflammatory lesions.

Before proceeding to a consideration of experimental and clinical segmental appendicitis it seems fitting to recall the classification of the main appendical arterial supply by Kelly and Hurdon, since anomalous vessels must be considered in evaluating our experimental and clinical data. These authors recognized four types of main appendical arteries:

1. A single vessel supplying the entire appendix but no portion of the cecum. It usually arises from the ileocolic artery. This type of blood supply is present in one third of the cases.

2. More than one vessel, the first arising as in type 1 and supplying the distal four fifths of the appendix. The proximal portion of the appendix is supplied by one or two branches of the posterior ileocecal artery. This type is present in one quarter of the cases.

3. One or more vessels supplying both the appendix and the adjacent cecum, arising from the posterior ileocecal artery. Ligation of the proximal appendical artery may result in necrosis of the cecum. This type occurs in one quarter of the cases.

4. Loop formation between the main arteries as in the mesentery. This type of blood supply is of rare occurrence.

The general anatomy, including the vascular supply, of the cecal appendage (hereafter referred to as the appendix) in the rabbit (Lepus cuniculus) is comparable to that of the human appendix. There are, however, approximately twelve secondary branches, and the main appendical vessel lies close to the edge of the organ. These branches communicate with a vessel which lies in the mesentery of the adjacent

7. Van Cott, in Fowler, G. R.: A Treatise on Appendicitis, Philadelphia, J. B. Lippincott Company, 1894.

8. Brunn, W.: Ueber das Segmentäre bei der Wurmfortsatzentzündung, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **21**:1, 1909.

9. Graham, G. S.: The Vascular Factor in Appendicitis, South. M. J. **20**:365 (May) 1927.

10. Seng, H., in Aschoff, L.: Appendicitis: Its Etiology and Pathogenesis, London, Constable & Co., Ltd., 1931.

ileum and runs parallel to it. The interior of the cecal pouch possesses a complete spiral valve, and the mucosa of the appendix is richly supplied with solitary acuminate lymph nodules.[11] The intramural branchings are similar to those seen in man, and there are no appreciable anastomoses between adjacent branches. They are, therefore, essentially terminal vessels.

EXPERIMENTAL METHOD

In our studies, as has been stated, rabbits were used. The general method of procedure was to anesthetize the animal by intravenous injection of pentobarbital sodium, 1 grain (0.06 Gm.) for each 5 pounds (2.3 Kg.) of body weight, after which the abdomen was prepared and the appendix exteriorized under the usual conditions of surgical asepsis. After ligation of the vessels with catgut, observations were generally made for a limited period on the exposed appendix, the organ being suitably protected by warm gauze pads. The appendix was then returned to the abdomen, and the laparotomy wound was closed and dressed. Subsequent studies were made at varying intervals, after which the animal was killed. In referring to the technical procedures a schematic drawing (fig. 1) will be used as a key, the numbers indicating the secondary branches, starting with

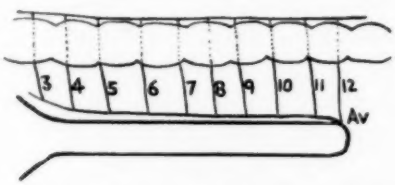

Fig. 1.—Vascular supply of the rabbit appendix. (Branches from AV to the appendix not shown.)

the base of the appendix. *A* and *V* refer to the main appendical artery and vein, respectively. Owing to the close proximity of the main artery and vein it was often difficult to ligate them separately without undue trauma. In the case of the secondary branches both vessels were always occluded together. It was deemed advisable to refer to the secondary vessels, starting with the distal, or no. 12, branch even though some variation in number occurred in a few of our experimental animals. Longitudinal sections of the appendix were used for histopathologic study.

EXPERIMENTAL EFFECTS OF LIGATION OF THE APPENDICAL VESSELS IN THE RABBIT

Ligation of the Main Appendical Artery and Vein and the Secondary Branches.

Rabbit 257.—Extent of occlusion: secondary branches 8, 9, 10, 11 and 12 and the main appendical artery and vein just proximal to branch 7.

Period of observation: eight hours.

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11. Huntington, G. S.: The Anatomy of the Human Peritoneum and Abdominal Cavity Considered from the Standpoint of Development and Comparative Anatomy, Philadelphia, Lea Bros. & Co., 1903.

Gross pathologic picture: There was hemorrhagic infarction of the distal portion of the appendix, with a striking, somewhat sinuous line of demarcation corresponding to the upper level of ligation. The lesion was segmental and appeared to involve chiefly the mucosa and submucosa. The serosa was apparently free from fibrin and purulent exudate. Distal segmental appendicitis was present.

Histopathologic picture: No sections were taken.

Rabbit 332.—Extent of occlusion: secondary branches 7, 8 and 9 and the main appendical artery and vein just proximal and distal to them.

Period of observation: nine hours.

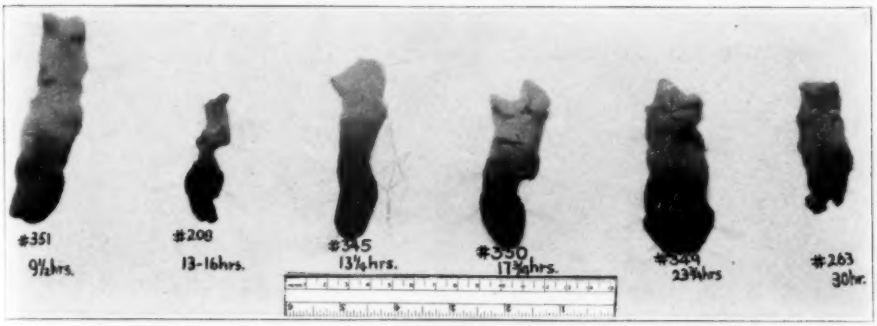

Fig. 2.—Experimental segmental appendicitis in the rabbit.

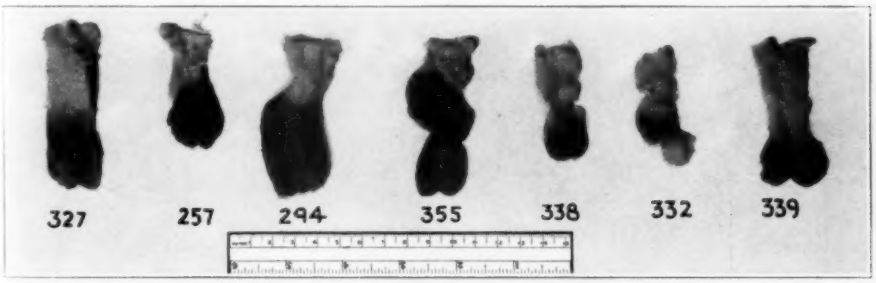

Fig. 3.—Experimental segmental appendicitis in the rabbit. Note the central lesion in the appendix of rabbit 332.

Gross pathologic picture: Immediately after ligation that portion of the wall directly opposite branches 7, 8 and 9 became cyanotic, the appendix distal to this area being mildly cyanosed. At the expiration of nine hours there were punctate and confluent hemorrhages, chiefly into the mucosa, which was clearly demarcated from the contiguous, normal-appearing pale tissue. The serosal vessels over the affected region were congested. The area of hemorrhagic necrosis corresponded to the distribution of secondary branches 7, 8 and 9. There was central segmental appendicitis.

Histopathologic picture: Longitudinal sections taken at the upper level of the junction of the diseased with the normal-appearing tissue revealed punctate hemorrhages into the mucosa, capillary congestion and extravasation of erythrocytes

into the subepithelial tissue. The lymph nodules were infiltrated with erythrocytes. The submucosa was edematous and contained numerous eosinophils and plasma cells.[12] The pathologic process appeared to be localized chiefly in the mucosa, in the form of punctate hemorrhagic necroses. The muscularis and the serosa were unaffected.

Rabbit 294.—Extent of occlusion: secondary branches 7, 8, 9, 10, 11 and 12 and the main appendical artery and vein just proximal to branch 7.

Period of observation: ten hours.

Gross pathologic picture: The terminal segment of the appendix, corresponding to the distribution of the occluded vessels, was gangrenous. The entire wall was thickened and hemorrhagic up to and possibly including the serosa. The serosa was covered with a thin purulent exudate which extended for a short distance proximal to the line of demarcation. There was distal segmental appendicitis.

Histopathologic picture: No sections were taken.

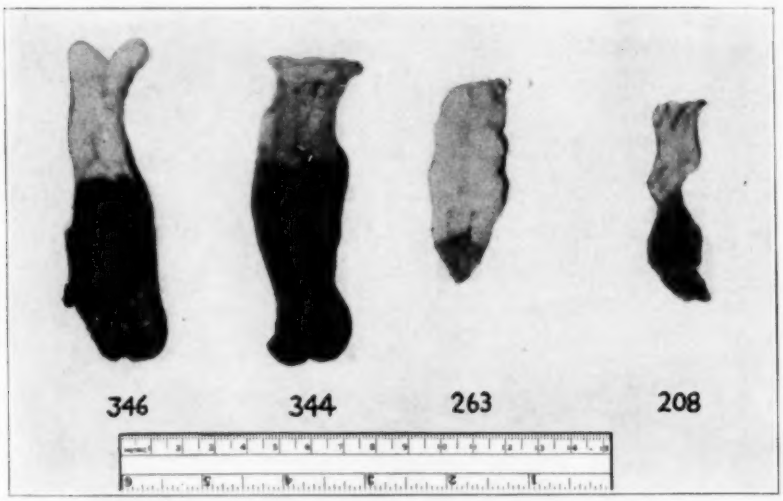

Fig. 4.—Experimental segmental appendicitis in the rabbit.

Rabbit 338.—Extent of occlusion: secondary branches 7, 8, 9, 10, 11 and 12 and the main appendical artery and vein at points between branches 5 and 6 (ligature 1) and branches 8 and 9 (ligature 2).

Period of observation: eleven and one-half hours.

Gross pathologic picture: Immediately after application of ligature 2 the appendix distal to this point became deeply cyanotic. Between ligature 1 and ligature 2 the wall was midly cyanosed, gradually tapering off into normal tissue as a point opposite ligature 1 was reached. There apparently was maintenance of some blood supply through unligated secondary branch 6, probably through minor anastomoses with branch 5. At the end of eleven and one-half hours the proximal lesion, i. e., that between ligature 1 and ligature 2, consisted of punctate and

12. A moderate number of eosinophils and plasma cells are seen in the normal rabbit's appendix. Only definite increases above the average are noted in the protocol.

confluent hemorrhages apparently limited to the mucosa, with slight increase in thickness of the wall. The distal segment exhibited hemorrhagic necrosis of the mucosa, with more pronounced thickening of the wall than the proximal lesion.

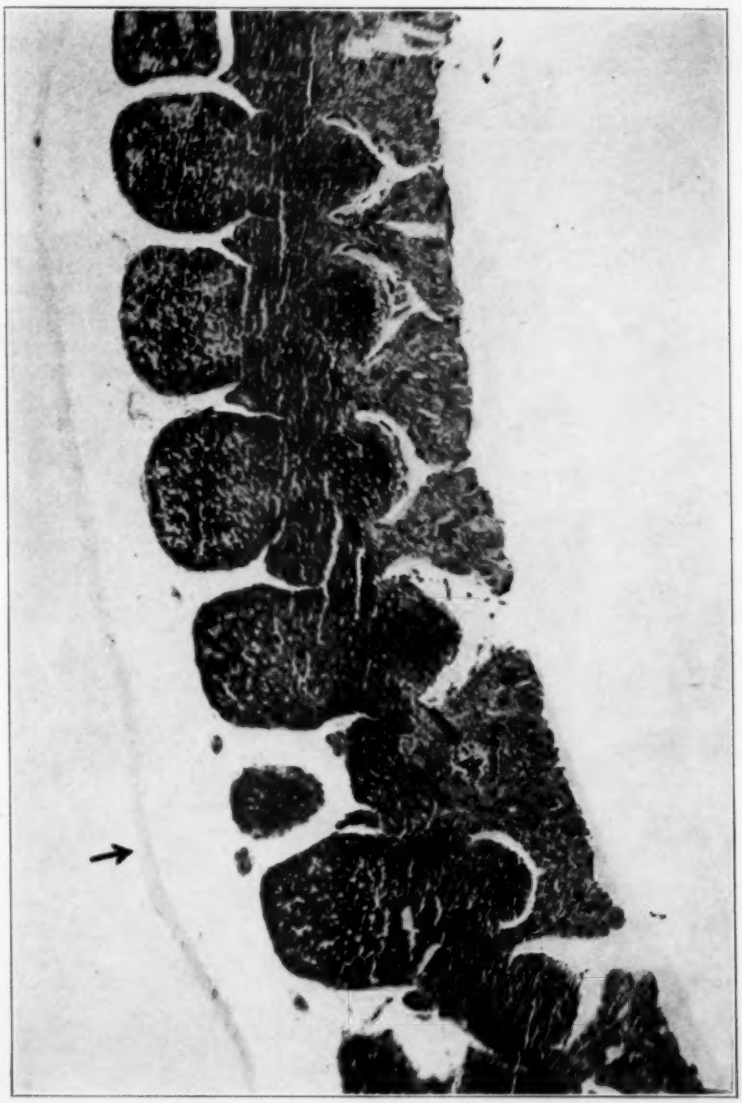

Fig. 5 (rabbit 332, ligation nine hours).—Hemorrhagic necrosis of the mucosa, submucosa and lymph nodules. The muscularis and serosa (see arrow) are unaffected. Note the denudation of the mucosa overlying the enlarged lymph nodules.

The deeper layers were also involved, but to a lesser degree. The serosa was dull in appearance and was edematous. There was distal segmental appendicitis, with a proximal lesion of a lesser degree of severity.

Histopathologic picture: Longitudinal sections taken at the level of junction of the proximal and the distal lesion revealed marked hemorrhagic necrosis of the apexes of the lymph nodules and overlying mucosa, the latter being entirely necrotic. There appeared to be an increase in eosinophils and plasma cells in

Fig. 6 (rabbit 338, ligation eleven and one-half hours).—Hemorrhagic necrosis of the mucosa and of the apexes of the lymph nodules (see arrows).

the submucosa, which was also edematous. There was some cellular infiltration of the muscularis and serosa, with congestion of the serosal vessels. The histopathologic changes of the proximal segment were distinctly milder and of lesser extent than those seen in the distal segment.

Rabbit 336.—Extent of occlusion: secondary branches 6, 7, 8 and 9 and the main appendical artery and vein just proximal and distal to them.

Period of observation: seventeen hours.

Gross pathologic picture: The middle portion of the appendix, corresponding to the distribution of the ligated vessels, was completely necrotic. There was hemorrhagic infarction of the entire wall in this area, which was segmentally and sharply delineated at both ends from the contiguous, normal-appearing tissue. The serosa overlying the necrotic tissue was covered with a thin purulent exudate. The wall in the area of segmental involvement was approximately one and one-half times the thickness of the adjacent appendical tissue. Some mucus was present in the appendical lumen distal to the region of pathologic involvement, and the mucosal vessels were congested. There was central segmental appendicitis.

Histopathologic picture: Longitudinal sections taken at the line of demarcation between the grossly pathologic and the normal-appearing tissue revealed a more advanced process than that seen in rabbit 338. There were large areas of hemorrhagic necrosis in the centers of the lymph nodules and in the interstitial tissue between the nodules. The mucosa was necrotic, and there was rather diffuse infiltration of the submucosa, the muscularis and the serosa with polymorphonuclear eosinophils and neutrophils, which also permeated the narrow spaces between the lymph nodules. The nodules were large and exhibited reticulum cell hyperplasia. Scattered mononuclear cells and plasma cells were also seen in the submucosa, which was edematous. The histologic picture showed a strikingly clear line of demarcation from the adjacent intact tissue.

Rabbit 355.—Extent of occlusion: secondary branches 7, 8, 9, 10, 11 and 12 and the main appendical artery and vein (*a*) just above branch 6; (*b*) between branches 8 and 9.

Period of observation: seventeen hours.

Gross pathologic picture: Distal to ligature 2 there was complete gangrene of the wall. Between ligatures 1 and 2 the tissue appeared thickened and intensely red. The necrosis appeared to be more superficial and less advanced than in the area distal to ligature 2. There was a sharp line of demarcation at the point of ligature 1, although just proximal to it the mucosa was hyperemic. The difference in the extent of pathologic involvement between the two areas described appeared to be due to the preservation of branch 6. There was distal segmental appendicitis.

Histopathologic picture: No sections were taken.

Rabbit 339.—Extent of occlusion: secondary branches 9, 10, 11 and 12 and the main appendical artery and vein proximal to branch 9.

Period of observation: twenty-one hours.

Gross pathologic picture: The distal segment of the appendix, corresponding to the distribution of the ligated vessels, was completely gangrenous and covered by a thin purulent exudate which extended proximal to the clear line of demarcation. There were fresh adhesions to adjacent loops of intestine. There was distal segmental appendicitis.

Histopathologic picture: The entire wall was diffusely infiltrated with polymorphonuclear neutrophils and eosinophils. There was advanced hemorrhagic infarction, with coagulation necrosis involving the mucosa and submucosa and extending between the lymph nodules. The latter were for the most part in a state of partial or complete disintegration. Their centers exhibited areas of focal necrosis which were filled with polymorphonuclear cells and were bordered chiefly by eosinophils extending to the periphery of each nodule. There was a

clear line of demarcation of the gangrenous from the contiguous intact tissue, but the inflammatory infiltration extended into the latter for some distance in the muscularis and serosa. In this region the mucosa, the lymph nodules and the interstitial tissue were entirely unaffected and contained only scattered eosinophils

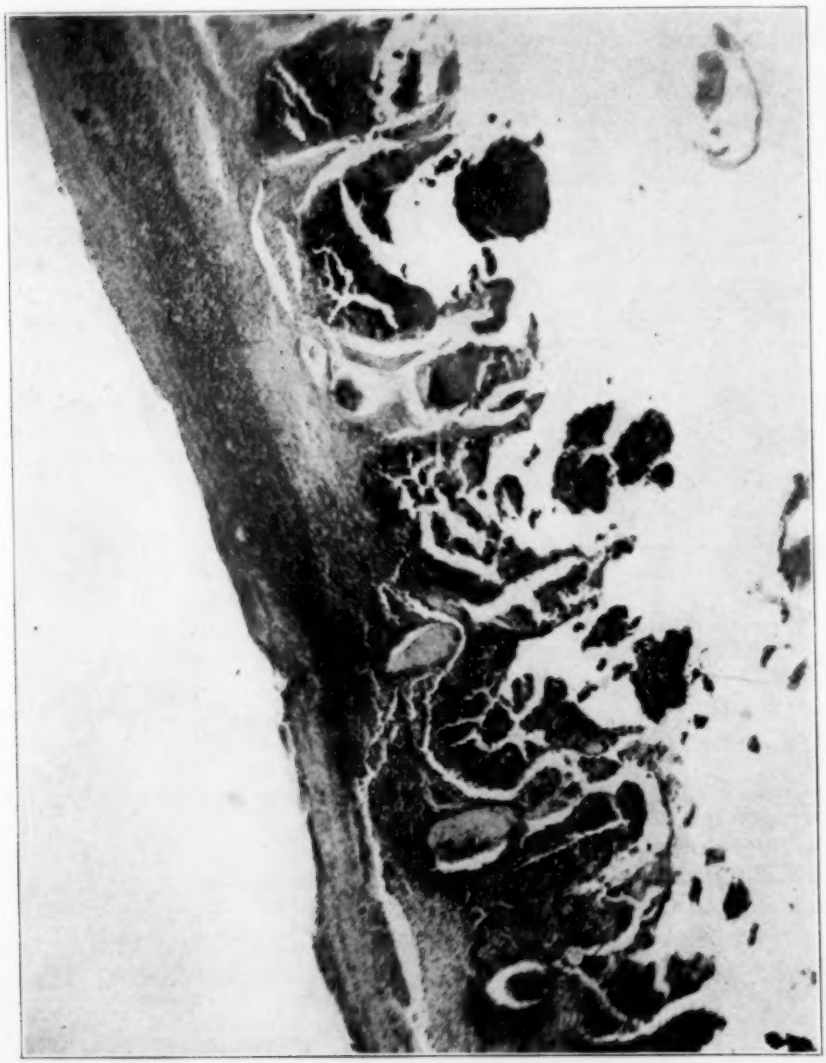

Fig. 7 (rabbit 327, ligation twenty-seven hours).—Photomicrograph showing the mucosa and most of the lymph follicles sloughed off in the gangrenous area.

as normally seen in the rabbit's appendix. The area of acute inflammation and necrosis was almost twice as thick as the region of infiltration of the muscularis and serosa, with normal mucosa and lymph nodules.

Rabbit 327.—Extent of occlusion: secondary branches 9, 10, 11 and 12 and the main appendical artery and vein proximal to branch 9.

Period of observation: twenty-seven hours.

Gross pathologic picture: There was gangrene of the distal segment which had been supplied by the occluded vessels. The wall was grayish black and thin owing to sloughing off of part of the necrotic tissue. In this area the lumen appeared slightly bulbous. A thick purulent exudate covered the serosa and extended beyond the clear line of demarcation to the contiguous nongangrenous area. Distal segmental appendicitis was present.

Histopathologic picture: The tissue changes were similar to those described for rabbit 339 (ligation, twenty-one hours) except that they were more advanced. Part of the acutely inflamed and gangrenous area had sloughed off, leaving this portion of the wall approximately one-half the thickness of the nongangrenous area adjoining. The latter, however, exhibited infiltration of the muscularis and serosa with inflammatory cells, the mucosa, the lymph nodules and the interstitial tissue being entirely unaffected.

Ligation of the Main Appendical Artery and the Secondary Vessels.

Rabbit 351.—Extent of occlusion: secondary branches 8, 9, 10, 11 and 12 and the main appendical artery proximal to branch 8.

Period of observation: nine and one-half hours.

Gross pathologic picture: There was sharply segmental hyperplasia of the lymph nodules, corresponding to the distribution of the ligated vessels. The lymph nodules projected prominently above the general level of the mucosa, appearing as pale elevations encompassed at their bases by salmon pink areas of injected vessels. The serosa was edematous and presented a delicate network of vessels, which appeared to be empty. There was early distal segmental appendicitis with lymphoid hyperplasia.

Histopathologic picture: The lymph nodules were elongated and projected prominently into the mucosa, which was denuded in places where it covered the follicles (fig. 5). The follicles exhibited hyperplasia and some eosinophilic infiltration, the latter extending into the interfollicular stroma. The submucosa, the muscularis and the serosa were edematous and infiltrated with polymorphonuclear neutrophils and eosinophils. There was some infiltration of the muscularis and the serosa by these cells for a distance beyond the visible area of hyperplasia of the lymph nodules.

Rabbit 208.—Extent of occlusion: secondary branches 9, 10, 11 and 12 and the main appendical artery proximal to branch 9.

Period of observation: thirteen to sixteen hours.

Gross pathologic picture: There was distal segmental hemorrhagic necrosis affecting principally the mucosa and the submucosa, corresponding in extent to the distribution of the ligated vessels. The serosa appeared uninvolved.

Histopathologic picture: Sections taken so as to include tissue from either side of the line of demarcation revealed necrosis of the mucosa, edema of the lymph nodules and infiltration of the serosa with polymorphonuclear neutrophils and round cells. The pathologic process was chiefly confined to the mucosa and submucosa. Sections taken near the tip of the appendix revealed a more advanced and deeper necrosis, with infiltration of the serosa by inflammatory cells. The muscularis appeared to be only slightly involved, its condition seeming out of proportion to the advanced pathologic change discernible in the other layers. There was marked vascular congestion.

Rabbit 350.—Extent of occlusion: secondary branches 8, 9, 10, 11 and 12 and the main appendical artery proximal to branch 8.

Period of observation: seventeen and three-quarters hours.

Gross pathologic picture: There was a segmental area of hemorrhagic necrosis apparently limited to the mucosa and part of the submucosa, corresponding in

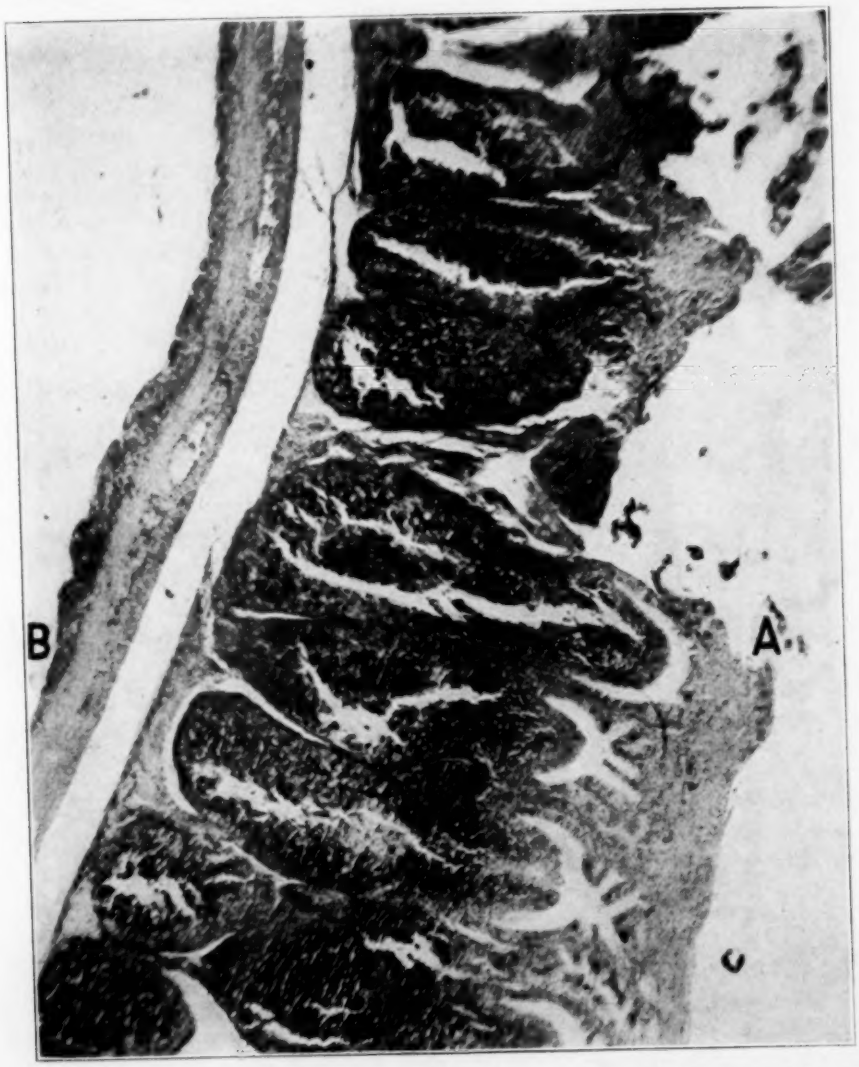

Fig. 8 (rabbit 327, ligation twenty-seven hours).—Edge of the segmental area of necrosis (*A*), showing the abrupt transition from uninvolved tissue; serosal involvement (*B*) beyond the edge of the segmental area of necrosis.

extent to the distribution of the ligated vessels. The serosa was ischemic, the arterial arborizations being devoid of blood. Distal segmental appendicitis was present.

Histopathologic picture: Longitudinal sections taken from the grossly involved area revealed hemorrhagic necrosis of the mucosa, edema and infiltration by neutrophils, eosinophils and plasma cells. Sections taken from a grossly uninvolved area a short distance above the line of demarcation showed no essential pathologic change.

Rabbit 349.—Extent of occlusion: secondary branches 7, 8, 9, 10, 11 and 12 and the main appendical artery proximal to branch 12.

Period of observation: twenty-three and three-quarters hours.

Gross pathologic picture: The serosa was covered with a thin purulent exudate for a short distance proximal to the line of demarcation which indicated the extent of hemorrhagic necrosis of the distal segment. The necrotic area corresponded to the distribution of the ligated vessels. The pathologic process appeared to be limited to the mucosa. Distal segmental appendicitis was present.

Histopathologic picture: The changes were practically identical with those seen in rabbit 263 (ligation, thirty hours) except that they were slightly less advanced.

Rabbit 263.—Extent of occlusion: secondary branches 7, 8, 9, 10, 11 and 12 and the main appendical artery proximal to branch 7.

Period of observation: thirty hours.

Gross pathologic picture: There was a segmental area of complete gangrene involving the portion of the appendix which had been supplied by the occluded vessels. The major and distal portion had sloughed off at a point 1 cm. from the line of demarcation, leaving only a small fragment of necrotic appendix attached to the intact portion. The serosa of the attached fragment was covered with purulent exudate which extended proximally for a short distance. The entire area of distal segmental appendicitis was completely walled off by the surrounding coils of the intestine and mesentery. The peritoneum contained a small amount of sanguineous fluid.

Histopathologic picture: Longitudinal sections taken at the point of junction of the attached necrotic tissue and the normal-appearing appendix revealed edema of the entire wall, coagulation and hemorrhagic necrosis of the mucosa, submucosa and lymph nodules. There was diffuse infiltration of the muscularis and serosa by inflammatory cells, without marked necrosis. As healthy tissue was approached there appeared some areas of punctate hemorrhagic necrosis within the lymph nodules, followed by interstitial hemorrhages which outlined the nodules clearly. No other pathologic change was discernible.

Ligation of the Main Appendical Vein and the Secondary Vessels.

Rabbit 292.—Extent of occlusion: secondary branches 7, 8, 9, 10, 11 and 12 and the main appendical vein proximal to branch 7.

Period of observation: twenty-three and one-half hours.

Gross pathologic picture: The distal segment of the appendix which had been supplied by the occluded vessels was filled with coagulated blood. The wall was approximately three times the normal thickness, and a purulent exudate covered the serosa proximal to the line of demarcation.

Histopathologic picture: No sections were taken.

Rabbit 346.—Extent of occlusion: secondary branches 8, 9, 10, 11 and 12 and the main appendical vein proximal to branch 8.

Period of observation: twenty-four hours.

Gross pathologic picture: The distal segment which had been supplied by the occluded vessels was the seat of a clearly defined area of infarction which

involved the entire wall. The latter was covered with a thin purulent exudate and appeared to be three or four times the normal thickness. There were liquid and coagulated blood in the lumen of the appendix, chiefly beyond the line of demarcation. Distal segmental appendicitis was present.

Histopathologic picture: The picture was much like that seen in the appendix of rabbit 263. There was a well defined line of demarcation which separated the healthy from the diseased tissue. In the necrotic segment the lymph nodules exhibited central areas of hemorrhagic necrosis, and the entire wall showed infarction and infiltration by polymorphonuclear cells. The zone of hemorrhagic necrosis gradually lessened as healthy tissue was approached, giving way to perinodular hemorrhages and finally to normal lymph follicles. The serosa showed an infiltrate of neutrophils, which extended for some distance into the grossly uninvolved area.

Rabbit 344.—Extent of occlusion: secondary branches 8, 9, 10, 11 and 12 and the main appendical vein proximal to branch 8.

Period of observation: twenty-five hours.

Gross pathologic picture: The entire wall was the seat of hemorrhagic necrosis corresponding in extent to the distribution of the vessels occluded. The wall was thickened in this area, and a small amount of free blood was seen in the lumen.

Histopathologic picture: No sections were taken.

Ligation of the Main Appendical Artery, the Main Appendical Artery and Vein and the Secondary Vessels.

Rabbit 345.—Extent of occlusion: secondary branches 5, 6, 7, 8, 9, 10, 11 and 12, the main appendical artery proximal to branch 5 (ligature 2) and the main appendical artery and vein between branches 10 and 11 (ligature 1).

Period of observation: thirteen and one-quarter hours.

Gross pathologic picture: Between ligatures 1 and 2 the appendical wall was ischemic and pale, the mucosa exhibiting some hemorrhage and pinpoint areas of necrosis. Beyond ligature 1 the tip of the appendix was black and completely necrotic. In the area distal to the point of ligation of the artery (ligature 2) necrosis was less advanced and more superficial than in the area distal to the point of ligation of both artery and vein (ligature 1). A clear line of demarcation separated the latter from the former, which, in turn, was somewhat less sharply demarcated from contiguous uninvolved tissue. Graded segmental appendicitis was present.

Histopathologic picture: The microscopic picture resembled that seen in rabbit 208 (approximately the same period after ligation of the main artery and secondary branches). Longitudinal sections taken from the necrotic tip of the appendix revealed involvement of all coats. The mucosa was completely necrotic; the lymph nodules were likewise involved at their upper poles; there was edema of the submucosa, and all coats, including the serosa, were infiltrated by polymorphonuclear cells.

Rabbit 333.—Extent of occlusion: secondary branches 9, 10, 11 and 12, the main appendical vein between branches 7 and 8 and the main appendical artery and vein proximal to branch 4.

Period of observation: twenty-four hours.

Gross pathologic picture: The extreme distal segment of the appendix was the seat of hemorrhagic necrosis corresponding to the distribution of the occluded secondary branches. The vascular supply of the proximal portion of the appendix appeared to have been maintained by the secondary branches above branch 9,

through the vessel which coursed behind the ileum. Ligation of the main appendical artery and vein proximal to branch 4 was apparently compensated for by this arrangement.

Histopathologic picture: No sections were taken.

Temporary Occlusion of the Main Appendical Artery and Vein with Ligation of the Secondary Branches.

Rabbit 340.—Extent of temporary occlusion: secondary branches 9, 10, 11, 12 ligated and main appendical artery and vein temporarily occluded proximal to branch 9.

Duration of occlusion of the main vessels: fourteen minutes' interruption, four minutes' release, ten minutes' reinterruption and then permanent reestablishment of circulation. The appendix was examined twenty-three hours later.

Gross pathologic picture: The appendix was taut, being distended with sanguineous material within the lumen. The contents were under increased pressure. The wall showed no gross pathologic change except at the extreme tip of the appendix where there was an area of focal necrosis measuring 0.5 cm. in diameter. This observation suggests the importance of the secondary branches in maintaining an adequate blood supply to the wall of the appendix.

Ligation of the Appendical Wall and Distention with Fluid.

Rabbit 374.—In this experiment the vessels were not ligated. Two sutures were placed at points about the proximal and distal thirds of the appendix, thus forming two closed sacs. Two cubic centimeters of sterile saline solution was injected into the lumen of the distal segment and 5 cc. into the lumen of the proximal segment. The pulsations in the main appendical artery disappeared almost immediately, and the organ appeared distended and pale. Nineteen and one-half hours later the serosa covering both sacs was covered by a thick purulent exudate. The appendix remained distended, and punctate areas of hemorrhagic necrosis were seen in the mucosa. It seemed probable that the pathologic involvement was due essentially to mechanical interference with the blood supply by distention and subsequent pressure on the wall, since absence of pulsation was noted immediately after the injection of saline solution. A possible but unlikely source of error is infection along the track of the hypodermic needle since this generally produces a more localized type of peritonitis.

Rabbit 348.—A single ligature was tried about a point at approximately the distal third of the appendix. Eight and five-sixths days later the appendix distal to the ligature appeared ruptured and gangrenous, and a localized abscess surrounded the remaining stump. Generalized peritonitis was present.

SUMMARY OF EXPERIMENTAL OBSERVATIONS

1. Ligation of the main vessels and secondary branches was followed by a sharply segmental type of appendical necrosis which, in general, corresponded to the distribution of the occluded vessels.

2. The degree and severity of the subsequent pathologic process depended on the extent of the vascular block and the duration of occlusion.

3. There appeared to be little difference in the results whether the main artery and vein were ligated singly or concomitantly with the secondary branches, except that a more hemorrhagic type of infarction

with free intraluminal blood was seen when the vein alone was occluded in addition to the secondary vessels.

4. The earliest segmental changes noted (eight to nine hours) were limited to the mucosa and submucosa. At ten hours the serosa was covered with purulent exudate.

5. Complete gangrene with sloughing of the affected segment occurred in approximately twenty-four hours after vascular occlusion.

6. Microscopic evidence of lateral extension of the inflammatory process beyond the line of demarcation was usually limited to the serosa, the overlying coats being unaffected.

7. The area of intramural spread of infection was wedge shaped, the base of the wedge being formed by the serosa.

COMPARATIVE STUDIES OF ACUTE SEGMENTAL APPENDICITIS IN MAN

Twenty cases of human segmental appendicitis have been chosen to illustrate the proximal, central and distal types of involvement. This division is only approximate since many specimens exhibit involvement of two contiguous segments. We have on rare occasions encountered a "skip" type in which the proximal and distal portions are involved and the central segment is intact.

The general frequency of the segmental type of involvement is suggested by the incidence of 17.5 per cent in our series of 200 cases of acute appendicitis.

The distribution of the cases with relation to age and sex was as follows:

	Decade				
Sex	1	2	3	4	5
Male 13	0	5	4	3	1
Female 7	2	3	1	1	0

Gross Pathologic Observations.—The gross pathologic findings are arranged in order of the duration of symptoms before the appendix was removed.

The duration of symptoms prior to operation varied from ten to forty-eight hours.

1. A woman aged 22 had had symptoms for ten hours. The appendix was 5 cm. in length. The serosal vessels were injected and the serosa was covered with a thin purulent exudate. The mucosa in the distal third was hemorrhagic and exhibited follicular ulceration. There was a clear line of demarcation separating this area from the adjacent tissue.

2. A boy aged 14 had had symptoms for ten hours. The appendix was 8 cm. in length. The serosa over the proximal two thirds was covered with purulent exudate. The segmental involvement was clearly apparent externally as well as

on the inner aspect, where the mucosa was hemorrhagic and ulcerated. The unopened appendix was dilated and tense in this area, and a fecalith was present.

3. A boy aged 11 had had symptoms for ten hours. The appendix was 10 cm. in length. The distal 6 cm. of serosa was covered with a purulent exudate, cor-

Fig. 9.—Vascular supply of the human appendix.

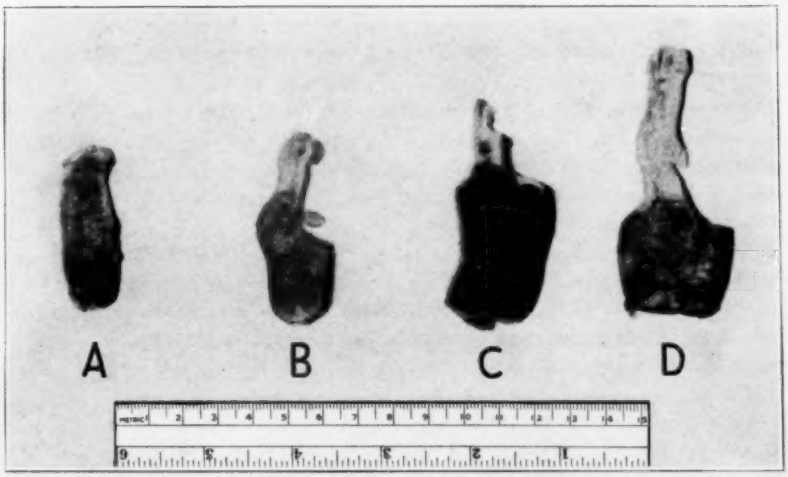

Fig. 10.—Human segmental appendicitis (*A*) in case 1, with symptoms of ten hours' duration, (*B*) in case 11, with symptoms of twenty-one hours' duration, (*C*) in case 6, with symptoms of fifteen hours' duration, and (*D*) in case 19, with symptoms of thirty-two hours' duration.

responding in its extent to underlying sharply segmental hemorrhagic necrosis of the mucosa. The wall was thickened in this area and the lumen slightly bulbous.

4. A man aged 25 had had symptoms for twelve hours. The appendix was 6 cm. in length. The serosal surface was covered with a thin purulent exudate,

most marked at the tip of the appendix. The wall was thickened and bulbous in the distal third, where the mucosa was the site of sharply segmental hemorrhagic necrosis.

5. A man aged 27 had had symptoms for thirteen hours. The appendix was 9 cm. in length. The lumen was filled with pus, and many fecaliths were present in the distal half, where the mucosa was necrotic. The serosal vessels were injected near the tip. It is of interest to note that at operation the appendix was distorted into the shape of the letter V owing to adhesions.

6. A man aged 31 had had symptoms for fifteen hours. The appendix was 7 cm. in length. The serosa was covered with a purulent exudate in its distal two thirds, where the wall exhibited a clear line of demarcation. The mucosa exhibited hemorrhagic infarction in the distal 6 cm., and the lumen was filled with liquid feces and fecaliths.

7. A girl aged 7 years had had symptoms for sixteen hours. The appendix was 7 cm. in length. The serosa in the distal half was covered with a purulent exudate. The wall in this area was thin owing to segmental hemorrhagic infarction and sloughing of the mucosa. At operation it was noted that in the region of distal segmental appendicitis the organ was distended and tense, and at the line of demarcation the lumen was obstructed by a fecalith.

8. A girl aged 15 had had symptoms for eighteen hours. The appendix was 6 cm. in length. The serosa in the distal third was covered with a thick purulent exudate, and corresponding to the location and extent of this condition there was a clearly segmental area of hemorrhagic necrosis on the mucosal surface.

9. A man aged 34 had had symptoms for eighteen hours. The appendix was 5 cm. in length. The serosa was covered with a thin purulent exudate. The wall was thickened, and the mucosa was hemorrhagic and necrotic in the middle third.

10. A man aged 50 had had symptoms for twenty-one hours. The appendix was 7 cm. in length. The serosa was covered with a thin plastic exudate in its middle third. The mucosa exhibited a segmental area of hemorrhagic necrosis in the distal half, where the wall was distinctly thickened. Several small intramural leiomyomas were present.

11. A man aged 26 had had symptoms for twenty-one hours. The appendix was 6 cm. in length. The entire wall in the central 3 cm. was the seat of hemorrhagic necrosis. In this area the wall was thinned and the mucosa sloughed off. The lumen in the distal 1 cm. was obliterated. At operation the appendix was found sharply angulated.

12. A woman aged 37 had had symptoms for twenty-two hours. The appendix was 6 cm. in length. The serosa was covered with a purulent exudate, and the mesenteriolar fat was thickened and indurated. The appendical wall was thickened and necrotic in its distal two thirds.

13. A girl aged 19 had had symptoms for twenty-four hours. The appendix measured 8 cm. in length. The serosa was covered with a thin purulent exudate. The wall was thin and necrotic in almost its entire length. The lumen contained several fecaliths.

14. A man aged 33 had had symptoms for twenty-four hours. The appendix was 8 cm. in length and curled to the shape of a letter U. The serosa of the distal 5 cm. was covered with a thin purulent exudate. There was segmental necrosis of the entire wall in this area, with a clear line of demarcation on the

mucosal surface. The involved portion of the canal was bulbous and contained several soft fecaliths and purulent material under slightly increased pressure. There were two vessels in the attached mesenteriolum, which appeared to be thrombosed. At a point 2 cm. from the proximal end there was stenosis of the lumen.

15. A man aged 29 had had symptoms for twenty-four hours. The appendix was 5 cm. in length. The serosa was covered with a purulent exudate, and the wall was gangrenous in its middle third, with a clear line of demarcation on either side. Mural thickening extended for a short distance beyond the area of segmental involvement.

16. A youth aged 19 had had symptoms for twenty-four hours. The appendix was 5 cm. in length. The serosa was covered with a plastic exudate in the distal two thirds. The wall was thickened throughout its length, and the distal half exhibited segmental hemorrhagic necrosis.

17. A youth aged 19 had had symptoms for twenty-four hours. The appendix was 7 cm. in length. The serosa was covered with a thin purulent exudate in the distal third. In this area the wall was thin, necrotic and pitted, with a clear line of demarcation at its junction with apparently normal tissue.

18. A girl aged 5 years had had symptoms for twenty-five and one-half hours. The appendix was 7 cm. in length. The wall was necrotic in its distal half, and the serosa was covered with a purulent exudate. There was a clear line of demarcation at the proximal end of the involved area.

19. A boy aged 12 had had symptoms for thirty-two hours. The appendix was 8 cm. in length. The distal third was the seat of segmental hemorrhagic necrosis and over this area the serosa was covered with a purulent exudate. The wall was thinned owing to the casting off of a gangrenous slough.

20. A girl aged 16 had had symptoms for forty-eight hours. The appendix was 6 cm. in length. The serosa was covered with a thick purulent exudate, and the wall was completely necrotic in the distal 5 cm. The mucosal aspect exhibited a sharply segmental area of involvement in the same location with advanced sloughing. Here the wall was thin and the lumen bulbous. There was a fecalith at the proximal line of demarcation.

Histologic Observations.—The general microscopic picture of acute segmental appendicitis in man follows closely the changes associated with the same condition in the rabbit. The early lesions are superficial and are limited chiefly to the mucosa and lymph nodules. The intramural spread of infection follows the general direction of the submucosal, intramuscular and intermuscular lymphatic networks until it reaches the serosa. It is wedge shaped and resembles the process of lymphatic extension in carcinoma of the bowel. The mucosal lesion is usually much smaller in extent than the serosal area of inflammation. The line of demarcation visible in the gross specimen exhibits the same sharply segmental type of necrosis in both rabbit and man. The time necessary for the production of complete necrosis of the appendix appears to be somewhat shorter in man than in the experimental animal. The discrepancy may be due, however, to the difficulty of establishing the exact time of onset of pathologic involvement.

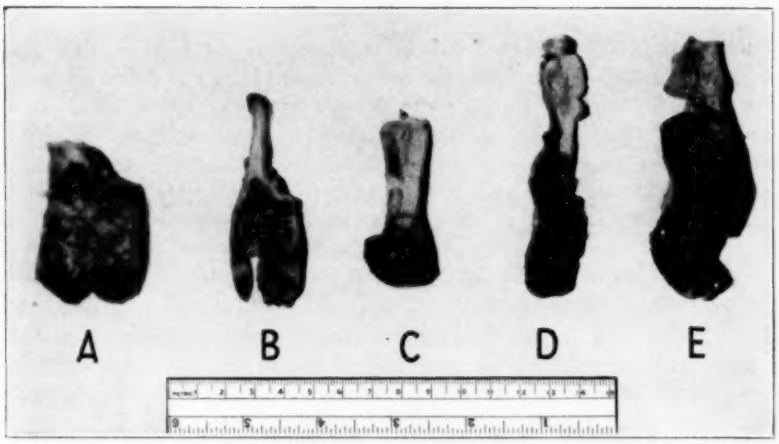

Fig. 11.—Human segmental appendicitis (*A*) in case 20, with symptoms of forty-eight hours' duration, (*B*) in case 2, with symptoms of ten hours' duration, (*C*) in a case not included in this report, with symptoms of forty-eight hours' duration, (*D*) in case 14, with symptoms of twenty-four hours' duration, and (*E*) in case 3, with symptoms of ten hours' duration.

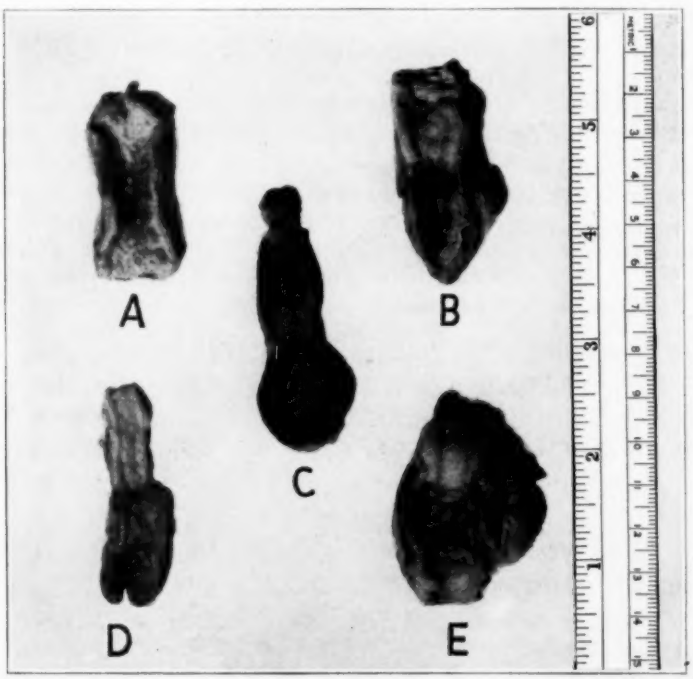

Fig. 12.—Human segmental appendicitis (*A*) in case 15, with symptoms of twenty-four hours' duration, (*B*) in case 16, with symptoms of twenty-four hours' duration, (*C*) in case 4, with symptoms of twelve hours' duration, (*D*) in case 9, with symptoms of eighteen hours' duration, and (*E*) in case 18, with symptoms of twenty-five and one-half hours' duration.

CORRELATION OF EXPERIMENTAL AND CLINICAL DATA

From an anatomicopathologic standpoint there are two obvious points of similarity between segmental appendicitis in the rabbit and the same condition in man. First, the vascular supply in both is of the terminal type. Second, the clearly defined segmental lesions produced by vascular ligation in the rabbit resemble both grossly and microscopically those

Fig. 13.—Photomicrograph (× 20) showing human segmental appendicitis in a case not included in this report. The section was taken at the line of demarcation. Note the abrupt loss of continuity of the epithelium at the edge of the necrotic area.

observed in man. The possible point of divergence lies in the pathogenesis. Are all segmental lesions in the human appendix due to vascular occlusion? If so, what is the etiologic explanation? Is there any relation to acute appendicitis in general? It is difficult to answer these

three questions with any degree of finality unless primary vascular occlusion can be proved to have occurred in each case. This necessitates careful taking of clinical histories, detailed observations by the surgeon

Fig. 14.—Photomicrograph (× 20) showing human segmental appendicitis in a case not included in this report. The section was taken at the line of demarcation. Note the intact lymph follicle at the top. The overlying epithelium is partly preserved and at the extreme bottom completely necrotic, together with the underlying mucosa.

and elimination of the possibility that vascular involvement may follow acute appendicitis instead of preceding it. Many divergent opinions

have been offered regarding the genesis of acute appendicitis. We shall attempt to reconcile these views with our hypothesis that acute segmental appendicitis in man is due to vascular occlusion.

Aschoff has postulated that acute appendicitis begins as a superficial localized lesion of the epithelium of the appendix, with the formation of a plug of leukocytes in a fold of the mucosa, usually in the distal portion. From this point there occurs a wedge-shaped spread to the

Fig. 15.—Photomicrograph (× 20) showing human segmental appendicitis in a case not included in this report. There is superficial necrosis. Note the rather sharp line of demarcation. In this region the mucosa and the lymph nodules are necrotic.

other coats, which are apt to be more extensively involved than the primary focal area. Aschoff further stated that the causative infecting organisms are brought to the appendix by the enterogenous route. These bacteria are apt to be gram-positive organisms, particularly diplococci and slender bacilli which Aschoff has admitted are normally present in the appendix. No explanation is offered as to why these normal inhabi-

tants suddenly acquire invasive tendencies. It is difficult to comprehend how an organ which is normally laved by pathogens or potential pathogens can be suddenly invaded unless some other factor becomes operative which permits intramural penetration.[13] It is probable that Aschoff's enterogenic theory and his description of the histopathologic process are correct up to the point of intramural invasion. If necrosis of the mucosa by direct contact of bacteria is the sole explanation of acute appendicitis it is difficult to explain acute mural involvement of an obliterated appendix in which no mucosa is seen. We have noted several such instances. Indirect evidence is presented by pharyngogenic hematogenous streptococcic peritonitis [14] and chronic bacillary dysentery. In the former disease foci of hemorrhagic intestinal necrosis has been noted in man and reproduced in the rabbit by intravenous injection of the organisms recovered from the throat. The intestinal lesions are secondary to the direct action of streptococci or their toxins on the mesenteric vessels within the wall of the intestine during the process of excretion from the blood stream into the lumen of the bowel and so out of the body. Nordlund [15] stated that in man there is a transient invasion of the blood stream by organisms from a primary focus in the throat. We believe that involvement of the peritoneum occurs through the areas of necrosis described, particularly since intramural penetration is indicated by the isolation of streptococci and of Bacillus coli from the peritoneal exudate. A case may be cited, that of a child, in which three separate areas of focal hemorrhagic necrosis occurred in the appendix, and on each was found a drop of greenish pus from which was isolated the same streptococcic strain as was present in the throat. In chronic bacillary dysentery [16] the primary ulcerative lesions are produced in the acute phase during the process of excretion of the dysentery toxin from the blood into the lumen of the bowel. The intestinal lesions can be reproduced by intravenous injection of the dysentery toxin alone. Secondary, nonspecific intramural invasion, particularly by enterococci and by B. coli, occurs during the chronic stage through the ulcers originally produced by the dysentery toxin. In one form of acute bacillary dysen-

13. Felsen, J.: Acute and Chronic Bacillary Dysentery, Am. J. Path. **12**:395 (May) 1936.

14. Felsen, J., and Osofsky, A. G.: Pharyngogenic Hematogenous Streptococcic Peritonitis, Arch. Surg. **31**:437 (Sept.) 1935.

15. Nordlund, U.: Ueber die sogenannte primäre kryptogenetische oder metastatisch Streptokokken Peritonitis, Ann. Acad. sc. fenn. (ser. A), 1933, vol. 38, no. 1.

16. Felsen, J.: The Relationship of Bacillary Dysentery to Distal Ileitis, Chronic Ulcerative Colitis and Nonspecific Granuloma, Ann. Int. Med. **10**:645 (Nov.) 1936.

tery, the appendical type,[17] the mucosa of the entire appendix is actually the site of punctate follicular necrosis without the development of acute suppurative appendicitis. Resolution takes place in the usual seven to ten day period just as it does in the ileum and colon. In the chronic stage it has been possible to demonstrate ulceration of the colon, ileum and appendix without evidence of acute appendicitis. The recent work of Altemeier,[18] who studied the bacterial flora in cases of acute perforating appendicitis, adds further doubt to the contention that the normal appendical bacteria, particularly B. coli and Enterococcus, can cause appendicitis without previous preparation by other factors. We therefore feel, as do other investigators, that there must be some additional agent which prepares the mucosal field before organisms normally present in the appendix can invade its wall. What is this factor?

Ricker [19] suggested that appendicitis begins as a circulatory disturbance of nervous origin which results in hemorrhagic infarction of the mucosa, through which a portal of entry is afforded the intraluminal bacteria. In mild involvement no appreciable lesion is produced, but in severe involvement necrosis of the mucosa occurs, secondary invasion of bacteria follows and gangrene results. Longhitano [20] stated the opinion that every acutely inflamed appendix previously has been the seat of a hematogenous embolic lesion. Surgeons have frequently noted thrombosed vessels in the mesenteriolum, with gangrene of the appendix below the point of obstruction.[21] They are commonly detected as the vessels are cut across, because no bleeding occurs. Various investigators have attempted to produce experimental appendicitis in rabbits by hematogenous or vascular occlusion. Beaussevat [22] concluded that while the disease can be produced by infection of the blood or of the lymph stream it is more commonly due to infection from the intestinal tract. Josue [23] produced appendicitis in rabbits by the intravenous injection of

17. Felsen, J.: Appendicular Form of Bacillary Dysentery, with Notes on Mesenteric Adenitis and Inflammation of the Distal Portion of the Ileum, Am. J. Dis. Child. **50**:661 (Sept.) 1935.

18. Altemeier, W. A.: The Bacterial Flora of Acute Perforated Appendicitis with Peritonitis, Ann. Surg. **107**:517 (April) 1938.

19. Ricker, G.: Der Stand der Lehre von der Epityphilitis, Deutsche Ztschr. f. Chir. **202**:125, 1927.

20. Longhitano, A.: La morphologia e la patologia del appendice vermiforme, Milano, A. Cordani, 1928; cited by Aschoff, L.: Appendicitis: Its Etiology and Pathogenesis, London, Constable & Co., Ltd., 1931.

21. Royster, H. A., in discussion on Wangensteen, O. H.; Buirge, R. E.; Dennis, C., and Ritchie, W.: Studies in the Etiology of Acute Appendicitis, Ann. Surg. **106**:910 (Nov.) 1937.

22. Beaussevat, M.: Appendicitis expérimentales, Rev. de gynéc. et de chir. abd. **1**:283, 1897.

23. Josue, O.: Appendicites, expérimentales par infection sanguine, Compt. rend. Soc. de biol. **49**:280, 1897.

streptococci without previous traumatization of the mucosa. Muhsam [24] ligated the appendical vessels of rabbits and succeeded in producing peripheral necrosis. Brunn's work on the experimental production of segmental inflammatory lesions of the appendix has already been described.

The concept of appendicitis as a focal manifestation of systemic infection, usually by the hematogenous route, has been proposed by Tripier and Paviot,[25] Grant,[26] Finney and Hamburger,[27] Rosenow [28] and others. Antecedent tonsillitis has often been credited with etiologic importance.[29] The so-called epidemic type of appendicitis has been described, particularly that following infections of the upper part of the respiratory tract. While the possibility exists that the direct enterogenous route may be followed by the invading organisms, our work points to the indirect hematogenous mechanism as an important and hitherto neglected factor.[30] Toxins, bacteria and heavy metals are excreted from the blood stream into the lumen of the bowel in this manner. Embolic lesions of the finer mesenteric radicals within the wall of the intestine are far commoner than thrombosis of the larger vessels. Toxins frequently act on the endothelium of the smaller blood vessels and produce necrosis with subsequent blockage. The chief route of excretion of lead from the blood stream is along the entire intestinal tract, with subsequent elimination in the feces. It is during this process of excretion of toxins and bacteria from the blood that the intramural structures are damaged and offer a focal point of entry for invading organisms. Intestinal lesions have been noted in association with many diseases, some of them possibly due to viruses. In addition to those previously referred to we would mention rheumatic intestinal necrosis, periarteritis nodosa and streptococcic, meningococcic, pneumococcic and staphylococcic bacteremias. The comparative rarity of acute appendicitis during intrauterine life and in newborn infants suggests the possibility of a protective immunizing mechanism transferred from the mother, which

24. Muhsam, R.: Ueber Appendicitisexperimente, Deutsche Ztschr. f. Chir. **55**:143, 1900.

25. Tripier, R., and Paviot, J.: L'appendicite par infection général, Semaine méd. **29**:73, 1899.

26. Grant, J.: Rare Forms of Gout and Rheumatism, Montreal M. J. **22**:341, 1893; M. Rec., New York **44**:609, 1893.

27. Finney, J. M. T., and Hamburger, L. P.: The Relationship of Appendicitis to Infectious Diseases, Am. Med. **2**:941 (Dec. 14) 1901.

28. Rosenow, E. C.: Bacteriology of Appendicitis and Production by Intravenous Injection of Streptococci and Colon Bacilli, J. Infect. Dis. **16**:240, 1915.

29. Relation of Tonsillitis to Appendicitis, 1893-1928, Bibliography 189, Library of the New York Academy of Medicine, Bibliographical Department, Oct. 23, 1928.

30. Felsen, J.: Intestinal Manifestations of Systemic Disease, Rev. Gastroenterol. **5**:114 (June) 1938.

appears to be operative against many diseases during this period. In the other extreme of life vascular occlusion may be due to organic changes associated with senility. Gatewood [31] stated that appendicitis in the aged is sometimes of embolic origin.

The relation of distention of the appendical lumen to acute appendicitis has been stressed by some investigators. Van Zwalenburg [32] occluded the appendical canal in the dog by means of a ligature and then injected fluid under high pressure. He concluded that when the "hydraulic pressure equal to the arterial tension is maintained within the lumen of the appendix for a short time it is promptly followed by typical appendicitis." The experimental studies of Wangensteen [33] and his co-workers along similar lines led them to conclude that distention is probably the most important factor in the production of experimental appendicitis. In carrying out the experiment of ligation of the appendical wall and distention with fluid on rabbit 374 we noted the almost instantaneous disappearance of pulsation in the main appendical artery. The natural assumption is that as a result of continued compression by the increased tension within the lumen the arterial supply was cut off and necrosis with infection of the involved segment followed. Bowers [34] concluded that acute appendicitis is a form of closed loop obstruction in the majority of cases. The appendix being essentially secretory, the segment obstructed distends and eventually ruptures. This possibility is illustrated by the appendixes in cases 2, 7, 14 and 20, in which either a stricture or a fecalith was observed at the line of demarcation.

The peculiar anatomic variations in the position of the human appendix and its rather free mobility render the theory of a mechanical vascular or luminal obstruction feasible. Twists or angulations by adhesive bands are conceivable (cases 5 and 11). Vascular obstruction may be only temporary, being due to a transient twist of the mesentery which would no longer be discernible at the time of operation. This is one of many difficulties which stand in the way of demonstrating conclusively the presence or absence of vascular occlusion in man. In some cases the surgeon makes no note of the presence or absence of thrombosed vessels, and insufficient mesenteriolum is supplied the pathologist to enable him to reach a definite conclusion. At times it is

31. Gatewood: Appendicitis in Old Age, M. Clin. North America **10**:303 (April) 1930.

32. Van Zwalenburg, C.: Obstruction and Consequent Distention the Cause of Appendicitis, as Proved by Cases and by Experimental Appendicitis in Dogs, J. A. M. A. **42**:820 (March 26) 1904.

33. Wagensteen, O. H.; Buirge, R. E.; Dennis, C., and Ritchie, W.: Studies in the Etiology of Acute Appendicitis, Ann. Surg. **106**:910 (Nov.) 1937.

34. Bowers, W. F.: The Role of Distention in the Genesis of Acute Inflammation of Hollow Viscera, Am. J. M. Sc. **194**:205 (Aug.) 1937.

impossible to state whether the thrombosis is primary or secondary. Careful histories and search for primary foci are woefully lacking in cases of acute appendicitis, thus making it impossible to trace some antecedent factor. In only 2 of the cases reported in this series was a preceding infection of the respiratory tract observed (cases 7 and 15). It becomes necessary, therefore, to rely on experimental data and parallel observations on the intestine in the presence of other diseases. Whether the blood vessels are affected by systemic toxins or by bacteria from a distant focus or whether they are obstructed secondarily by distention of the lumen, by angulation or by foreign bodies, the theory of vascular occlusion as the cause of segmental appendicitis seems plausible. The applicability of this theory to the pathogenesis of appendicitis in general is also suggested by the data herein presented.

SUMMARY AND CONCLUSIONS

The general concept of segmental appendicitis is described.

Lesions similar to those seen in man have been produced in the rabbit by vascular occlusion.

An attempt has been made to reconcile the various theories regarding the cause of appendicitis with the theory of vascular occlusion, which we hold to be true in the case of acute segmental appendicitis.

INCARCERATED MECKEL'S DIVERTICULUM IN FEMORAL HERNIA

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Johann Friedreich Meckel [1] was the first to describe a congenital diverticulum of the lower portion of the ileum. His description was published in 1808. He called attention to the importance of this structure in causation of serious disease. One hundred and fifteen years before this report, in 1683, Ruysch [2] had described a diverticulum and later in 1701 had published in "Thesaurus Anatomicus" (vol. 7, fig. 283) an illustration of this malformation. In 1700 Littré [3] reported a diverticulum encountered in a hernial sac. He, however, failed to describe the muscular coats characteristic of the congenital defect, and the embryonic derivation was not traced. It was from this description that the term "Littré's hernia" took origin.

Meckel's diverticulum, an anomaly found in man, occurs rather commonly. Various opinions have been expressed as to its incidence. The estimates range from 0.1 to 3 per cent. Balfour [4] found 15 Meckel's diverticula in 11,107 abdominal operations (0.1 per cent). Routine exploration, however, was not performed in this series. Cunningham in his "Textbook of Anatomy" [5] stated that Meckel's diverticulum was present in 73 of 3,302 cadavers (2.2 per cent). Schaetz [6] found 17 diverticula in 737 cadavers (2.3 per cent). In 10,300 necropsies,

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From Surgical Service *A* of St. Luke's Hospital.

Read at the clinical meeting of the Chicago Surgical Society at St. Luke's Hospital, March 5, 1938.

1. Meckel, J. F.: Ueber die Divertikel am Darmkanal, Arch. f. d. Physiol. **9**:421-453, 1808.

2. Ruysch, cited by Mixter, C. G.: Meckel's Diverticulum and Its Surgical Significance, Proc. Inst. Med. Chicago **9**:286-308, 1933.

3. Littré, cited by Mixter, C. G.: Meckel's Diverticulum and Its Surgical Significance, Proc. Inst. Med. Chicago **9**:286-308, 1933.

4. Balfour, D. C.: Meckel's Diverticulum: A Report of Fifteen Cases, J. Minnesota State M. A. **31**:110-112, 1911.

5. Cunningham, D. J.: Textbook of Anatomy, ed. 5, New York, William Wood & Company, 1923, p. 1200.

6. Schaetz, G.: Beiträge zur Morphologie des Meckel'sche Divertikels, Beitr. z. path. Anat. u. z. allg. Path. **74**:115-293, 1925.

Turner [7] found 81 (0.8 per cent). Forque and Riche [8] noted 112 in 7,850 necropsies (1.4 per cent), and Kelynack [9] found 18 in 1,446 cadavers (1.2 per cent). Mitchell [10] found 39 in 1,635 necropsies (2.4 per cent); Harkins [11] reported 41 in 2,400 necropsies (1.7 per cent). The incidence of Meckel's diverticulum in these investigations is 1.3 per cent.

The diverticulum exists because of failure of the vitelline duct to become obliterated. This process of closure usually occurs at the seventh week of embryonic development. Failure of the complete process of atrophy of the ducts results in Meckel's diverticulum, or umbilical anus.

Many have been found in postmortem examinations that had never given symptoms. Complications of Meckel's diverticulum are few. It has been estimated that about 15 to 20 per cent of all the diverticula are diagnosed (Faust [12]). Christie [13] in studies on infants found that complications were present in 15.8 per cent of cases. The chief complications were inflammation and peritonitis. Faust [12] stated that in a twenty-one year period at the Mayo Clinic Meckel's diverticulum was encountered 135 times. In about 30 per cent of cases it was definitely diseased and was of clinical significance. Some estimate of its infrequency as a source of symptoms in the diseases of childhood is obtained from the experience of Mixter.[14] He stated that while 32 patients were operated on for Meckel's diverticulum, 1,815 appendectomies and 2,674 herniorrhaphies were done in the same period.

When a pathologic process does exist in this structure, however, the most common findings are: (1) diverticulitis; (2) hemorrhage; (3) intestinal obstruction, and (4) incarceration in an umbilical or inguinal hernia or (rarely) in a femoral hernia.

Femoral hernia also occurs rather commonly. This type of hernia is not nearly as common as inguinal hernia, but it frequently occurs in association with the latter and passes unrecognized unless the region is carefully examined. Andrews [15] drew attention to the fact that many

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7. Turner, cited by Doolin, W.: Acute Abdominal Emergencies Due to the Presence of Meckel's Diverticulum, Irish J. M. Sc. **43**:299-305, 1929.

8. Forque, E., and Riche, V.: Le diverticulae de Meckel, Paris, Octave Doin, 1907.

9. Kelynack, T. N.: On Meckel's Diverticulum, Brit. M. J. **2**:459-466, 1897.

10. Mitchell, L. J.: Notes on a Series of Thirty-Nine Cases of Meckel's Diverticulum, J. Anat. & Physiol. **32**:675-678, 1898.

11. Harkins, H. N.: Intussusception Due to Invaginated Meckel's Diverticulum, Ann. Surg. **98**:1070-1095, 1933.

12. Faust, L. S.: Meckel's Diverticulum with Unusual Clinical Manifestations, M. Clin. North America **15**:1483-1489, 1932.

13. Christie, A.: Meckel's Diverticulum: A Pathologic Study of Sixty-Three Cases, Am. J Dis. Child. **42**:544 (Sept.) 1931.

14. Mixter, C. G.: Meckel's Diverticulum and Its Surgical Significance, Proc. Inst Med. Chicago **9**:286-308, 1933.

15. Andrews, E. W.: Personal communication to the authors.

recurrences of inguinal hernia are wrongly diagnosed and are preexisting femoral hernias which were overlooked by the surgeon at the time of the surgical repair. The incidental ratio of femoral hernia to inguinal hernia is about 1:25 (Watson [16]).

Protrusion of Meckel's diverticulum through a hernial opening is not a great rarity. In 1924, Watson [16] was able to collect 147 cases from the literature. The vast majority of such hernias occur in the inguinal region. Ninety-six of this series accompanied inguinal hernias, and 34 accompanied femoral hernias. It is, therefore, unusual to observe the combination of a femoral hernia and Meckel's diverticulum. A review of the literature since 1700 reveals 16 cases of Meckel's diverticulum incarcerated in femoral hernia (Sweet [17]). Fourteen were reported prior to Jan. 1, 1929, and Sweet [17] and Donati [18] have each added 1 case since that time. Two cases of Meckel's diverticulum incarcerated in a femoral hernia have been observed at St. Luke's Hospital since 1933. We shall briefly review the records of these 2 cases.

REPORT OF CASES

CASE 1 (Dr. McArthur).—A woman aged 72 entered St. Luke's Hospital with a history of nausea of sixteen hours' duration and of swelling in the right inguinal region of twenty-two hours' duration. The patient had known of a swelling the size of an English walnut in the right inguinal region for five years. In walking about the house she slipped, falling to the floor. At that time she felt a snap in the right inguinal region and noticed that the swelling had increased to the size of a hen's egg. About six hours later she became nauseated and vomited small quantities on three or four occasions. At no time was there pain in the region of the swelling.

Physical examination on admission to the hospital revealed a temperature of 99.6 F. and a pulse rate of 68. The blood pressure in millimeters of mercury was 168 systolic and 80 diastolic. The erythrocytes numbered 3,600,000 and the leukocytes 16,000 per cubic millimeter of blood. The value for hemoglobin was 14.23 Gm. per hundred cubic centimeters of blood. The differential blood count was normal, and examination of the urine gave negative results.

With the patient under ethylene anesthesia an oblique inguinal incision was made. The mass encountered was a portion of small bowel tightly covered with omentum. When the strangulated bowel was released the color quickly returned to normal, and the bowel was replaced in the abdomen. The hernial opening was closed with interrupted chromic catgut sutures. The postoperative course was uneventful for thirty-six hours, after which time the patient began vomiting small quantities of small bowel contents. A nasal tube was placed into the stomach and suction applied. One thousand and ninety cubic centimeters of small bowel contents was recovered in three hours. A secondary operation was performed forty hours after the first.

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16. Watson, L. F.: Hernia, St. Louis, C. V. Mosby Company, 1924, p. 660.

17. Sweet, R. H.: Incarceration of a Meckel's Diverticulum: Review of the Literature, New England J. Med. **202**:997-998, 1930.

18. Donati, G. S.: Strangulation of Meckel's Diverticulum in a Right Crural Hernia, Policlinico (sez. chir.) **38**:278-287, 1931.

Through a right paramedian incision made with the patient under ethylene anesthesia, many dilated coils of ileum were encountered. These were followed to a collapsed area which was attached to the parietal peritoneum at the right femoral ring. When this attached bowel was released it was noted that instead of the ileum it was a projection from the ileum, or Meckel's diverticulum. About 5 inches (12.5 cm.) of bowel, including the diverticulum, was resected, and an end to end anastomosis was made. Recovery of the patient was without further complications, and she was discharged fourteen days after the second operation. Doolin[19] in 1929 reported a similar case except that the hernia was inguinal rather than femoral.

CASE 2 (Dr. Strohl).—A woman aged 48 entered St. Luke's Hospital because of a painful mass of ten hours' duration in the right inguinal region. She stated that she knew of a mass the size of a golf ball which had been present for several months. While doing her usual household duties she suddenly noticed a dull pain in the right inguinal region. She noticed an increase in the size of the mass concurrently with the onset of the pain.

Physical examination on admission revealed a temperature of 100.2 F. The pulse rate was 84. The blood pressure in millimeters of mercury was 122 systolic and 74 diastolic. The erythrocytes numbered 4,350,000 and the leukocytes 9,800 per cubic millimeter of blood. The hemoglobin determination revealed 14.6 Gm. per hundred cubic centimeters of blood. Examination of the urine gave negative results. The patient was put to bed with the foot of the bed elevated 15 inches (38 cm.). An ice pack was applied to the right inguinal region. One-sixth grain (0.01 Gm.) of morphine sulfate was given hypodermically at intervals of four hours. At the end of eight hours an unsuccessful attempt at reduction was followed within fifteen minutes by vomiting of 100 cc. of small bowel contents. Operation was immediately decided on as the course of choice. With the patient under ethylene anesthesia an oblique inguinal incision was made. The underlying tissue was edematous, but no adhesions were encountered. In careful examination of the bowel projecting through the femoral ring it was found to be projecting from the ileum and to be obviously Meckel's diverticulum. When the bowel was released there were no signs of vascular damage. The bowel was freed at its exit through the femoral ring, and the diverticulum was replaced in the abdomen. The hernial opening was closed with interrupted chromic catgut sutures. It has been said that Meckel's diverticulum is but a slightly greater menace than is the vermiform appendix. However, it was not thought justifiable to open the abdomen merely to resect an asymptomatic diverticulum present since birth in a patient 48 years of age. The postoperative convalescence was uneventful, and the patient left St. Luke's Hospital on the fourteenth postoperative day.

SUMMARY

In the total number of 18 cases of incarcerated Meckel's diverticulum in femoral hernia, it is interesting to note that 15 of the patients were women. It is not, however, a fair assumption to conclude that Meckel's diverticulum is more common in females than in males because of this observation alone.

19. Doolin, W.: Acute Abdominal Emergencies Due to the Presence of Meckel's Diverticulum, Irish J. M. Sc. **43**:299-305. 1929.

Another interesting fact is that the first recovery from Meckel's diverticulum incarcerated in a femoral hernia did not take place until 1885. In 15 of the 18 cases operation has been done with 2 deaths, or a mortality rate of 13.3 per cent. In the first 3 cases the condition was observed in postmortem examination, the cause of death being generalized peritonitis.

The procedure of choice, (Rogers,[20] Harrington[21] and Christopher[22]) when such a condition is found is to release the obstruction, repair the hernia and make an abdominal approach for dealing with the diverticulum.

With the addition of these 2 cases the total number of reported cases now stands at 18.

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20. Rogers, L.: Treatment of Strangulated Femoral Hernia, Am. J. Surg. **5**: 280-281, 1938.

21. Harrington, S. W.: Strangulated Meckel's Diverticulum in a Right Femoral Hernia, S. Clin. North America **6**:1188-1190, 1926.

22. Christopher, F.: Ileocolic Intussusception with Meckel's Diverticulum, S. Clin. North America **10**:347-349, 1930.

ROLE OF THE RESPIRATORY TRACT IN CONTAMINATION OF AIR

A COMPARATIVE STUDY

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HERMAN M. SCHIEBEL, M.D.
DURHAM, N. C.

In a previous publication by one of us (D. H.) [1] it was noted that the number of staphylococci in the air of an operating room varies directly with the number of occupants. On several occasions throughout the year cultures of material from the noses and throats of the operating room personnel were made, and it was found that contamination of the air with Staphylococcus aureus varied directly with the number of carriers of this organism and the density of the growth in the nasopharynx. A group selected at random from the general population on one occasion showed about the same percentage of carriers as had been found among the personnel of the operating room. During the winter of this year (1933-1934) the number of carriers at times ran as high as 80 per cent.

During the past year, sediment from the air of the operating room has been cultured weekly (chart 1). The number of colonies of Staph. aureus haemolyticus as well as the total number of colonies of all organisms per Petri dish was much lower than during the winter of 1933-1934, when our first cultures were made.[1] During the past year the average number of carriers of Staph. aureus in the nose and throat was not above 15 per cent, as compared with a maximum of 80 per cent when the higher degree of contamination of air was present (in 1934).

We have determined repeatedly by cultures that when occupancy is terminated the air becomes progressively more free of sedimenting viable bacteria even when electric fans are used to agitate the air. The rapidity with which the air becomes free of these sedimenting bacteria is illustrated by chart 2. Although in this chart we have no accurate record of the length of time the room had been vacant, in general it was occupied

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From the Department of Surgery, Duke University School of Medicine, and Duke Hospital.

1. Hart, D.: Operation Room Infections, Arch. Surg. **34**:874-896 (May) 1937.

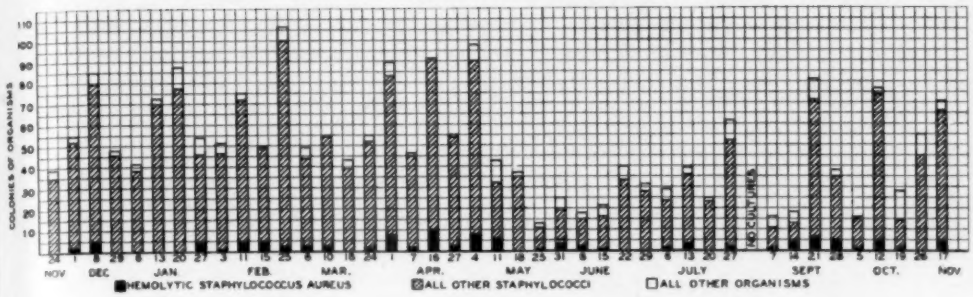
COLONIES OF ORGANISMS
NO CULTURES
NOV DEC JAN FEB MAR APR MAY JUNE JULY SEPT OCT NOV
HEMOLYTIC STAPHYLOCOCCUS AUREUS
ALL OTHER STAPHYLOCOCCI
ALL OTHER ORGANISMS

Chart 1.—Weekly cultures of sediment from the air of an operating room during occupancy, showing the prevalence of staphylococci and other organisms settling on a Petri dish of blood agar during an exposure of one hour. All plates were incubated for forty-eight hours at a temperature of 37.5 C. The colonies were then identified and recorded. Organisms other than staphylococci were few, were all relatively nonpathogenic and in this chart are grouped together for simplicity. Note the fluctuations in the number of organisms, particularly the great reduction during the warmer months. Staph. aureus haemolyticus appeared frequently but in relatively small numbers. At times this organism may be more numerous; it has caused the majority of the operating room infections coming under our observation. Such infections in clean primary incisions have been all but eliminated by sterilization of the air in the operating room.[5b]

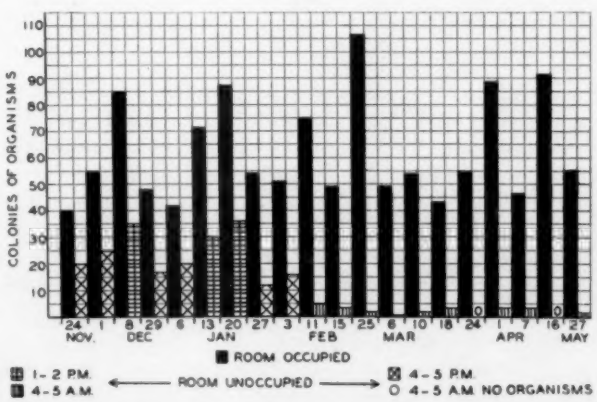

Chart 2.—Weekly cultures of sediment from the air in an operating room, showing the rapid reduction in the number of organisms settling from the air with cessation of occupancy. Each culture was made by exposure of a Petri dish of blood agar for one hour. This was incubated for forty-eight hours, and the colonies were then identified and recorded. This chart shows only the total number of organisms. In both the occupied and the unoccupied room the proportions were approximately the same as are shown in chart 1.

While the time since occupancy cannot be accurately given each week, in general the room was occupied until near noon and was not used during the afternoon or night when these cultures were made. No culture was made immediately after termination of occupancy.

until about noon, was not used during the afternoon or night when cultures were to be made and was never tested immediately after occupancy was terminated. It has been observed that with resumption of occupancy there is rapid recontamination of the air. When adjacent rooms and corridors are occupied there is a slight to moderate rise in contamination in a closed, unoccupied operating room, indicating some transmission of organisms by air currents through cracks under and around doors or through openings that cannot be closed tightly.

Before we began sterilization of the air in the operating room it was our policy for a number of years to postpone extensive operative procedures, such as thoracoplasties, until the summer, in order to avoid the greater risk of infection during the periods of greatest contamination of air. At all times such important operative procedures were performed in the morning in a room which had been unoccupied for at least twelve hours and which contained as few occupants as possible during the operation. We felt that the greatest source of pollution of the air was the nose and throat and not the skin or the incoming air, though both of these may at times be of some significance. This opinion was based on our cultural studies showing the relation between the presence of Staph. aureus in the noses and throats of the operating room personnel and the degree of contamination of air [1] and on the published reports showing the relation between the presence of streptococci in the nasopharynxes of the operating room personnel and the prevalence of wound infections caused by this organism.[2]

In order to determine more accurately the relation between the flora of the nose and throat and contamination of the air, it was decided to make a comparative study extending over a year. Ten men who spent most of each day in one room were selected. At weekly intervals during the last hour of the day's occupancy a Petri dish of blood agar was exposed to sedimentation from the air. During and at the end of this time material from the nose and throat of each occupant was cultured as follows:

The mucous membranes were swabbed with an ordinary cotton applicator. This was washed in 10 cc. of broth. The resultant suspension was diluted 1:100, and 0.1 cc. of this dilution was added to 10 cc. of agar and 2 cc. of blood and poured as a plate. All cultures were incubated for forty-eight hours at 37.5 C. The colonies were then identified and recorded.

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2. (*a*) Meleney, F. L.: Seasonal Incidence of Hemolytic Streptococcus in the Nose and Throat, in Surgical Operating Personnel: Significance of Masking During Operation, J. A. M. A. **88**:1392-1394 (April 30) 1927. (*b*) Meleney, F. L., and Stevens, F. A.: Postoperative Haemolytic Streptococcus Wound Infections and Their Relation to Haemolytic Streptococcus Carriers Among the Operating Personnel, Surg., Gynec. & Obst. **43**:338-342 (Sept.) 1926. (*c*) Meleney, F. L.: Infection in Clean Operative Wounds: A Nine Year Study, ibid. **60**:264-276 (Feb. 15) 1935. (*d*) Walker, I. J.: How Can We Determine the Efficiency of the Surgical Mask? ibid. **50**:266-270 (Jan., no. 1A) 1930.

In making the cultures of material from the air, sedimentation was used rather than the air centrifuge method of Wells,[3] since it was felt that this would give a more accurate estimate of the number of organisms which might settle on the sterile supplies and on the open wound.

Certain difficulties were encountered, such as the fact that Streptococcus viridans alpha is not found viable as a surface colony on the blood agar plate exposed in the room, although it may be obtained by other methods. Staphylococcus albus was the organism most frequently cultured on the open plate, while Str. viridans alpha was most commonly found in the nose and throat. The relative rise and fall of the level of contamination by Str. viridans alpha shown in the cultures of material from the throat was, however, fairly well paralleled not only by the rise and fall of the level of contamination by Staph. albus in the nose and throat but also by the number of colonies of Staph. albus

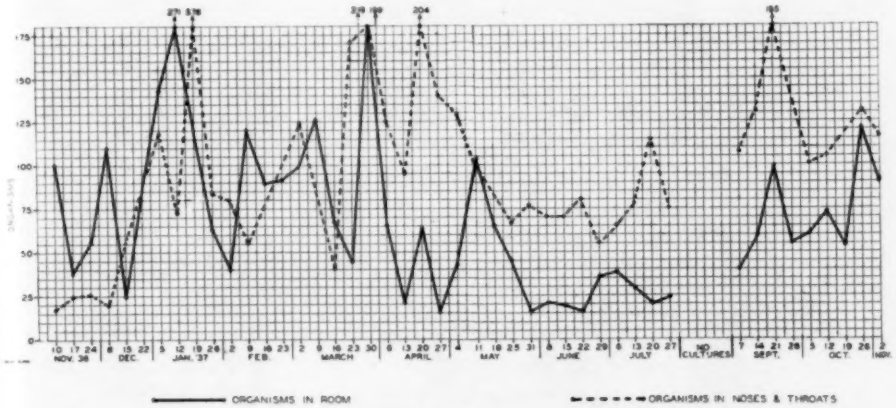

Chart 3.—Weekly cultures showing the relation between the number of organisms in the air of an occupied room and the degree of contamination of the noses and throats of the occupants. Our records show the total number of colonies of each organism (see chart 4 for Staph. aureus haemolyticus), but the proportions were approximately the same as those given in chart 1, and the curves were roughly parallel; to preserve the simplicity of the chart, therefore, only the totals are given. The low degree of contamination of the air and the high degree of contamination of the nasopharynx during April are explained by a drop in the number of organisms in the nose and throat except for Str. viridans alpha, which continued to be present in large numbers and which is not recovered from the air as a surface colony on blood agar.

sedimenting from the air. (For exception see chart 3.) In general the number of colonies of staphylococci (which are easily cultured on an open plate) can be taken as an index of the degree of contamination of

3. Wells, W. F., and Wells, M. W.: Air-Borne Infection, J. A. M. A. **107:** 1698-1703 (Nov. 21) 1936; Air-Borne Infection: Sanitary Control, ibid. **107:**1805-1809 (Nov. 28) 1936.

air. The total number of all organisms cultured from the air of the room roughly parallels the total number cultured from the noses and throats of the occupants (chart 3).

Chart 4 indicates the days on which Staph. aureus haemolyticus appeared in the cultures of material from the air or the nasopharynx or both and the comparative number of organisms present in each place. This organism was grown from the nasopharynx or from the air of the room or both on twenty-two occasions during the making of the cultures. On 16, or 73 per cent, of these occasions they were present in both places at the same time. In 3 cultures they were obtained from the nose and throat and not from the air of the room, and on three occasions they were found in the air but not in the nose and throat.

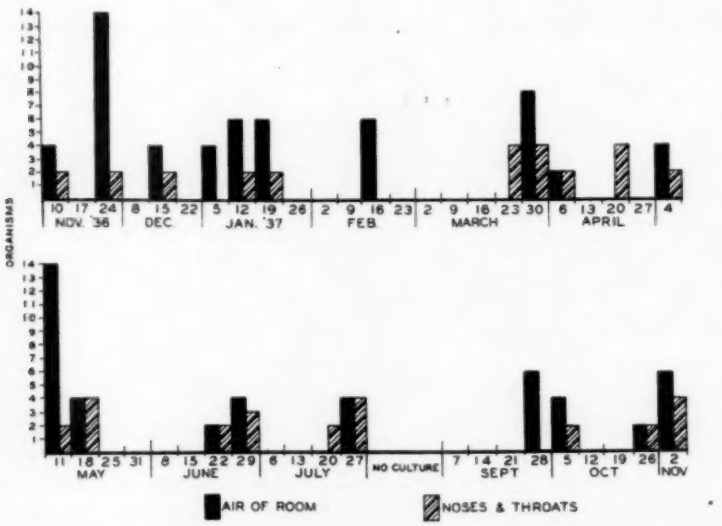

Chart 4.—Weekly cultures showing the correlation between the prevalence of Staph. aureus haemolyticus in the air of an occupied room and its presence in the noses and throats of the occupants. Forty-five cultures were made at weekly intervals, with the following results: Cultures of sediment from the air and cultures of material from the nasopharynx were similar in 87 per cent of instances. Staph. aureus haemolyticus was present in both in 36 per cent and absent in both in 51 per cent of instances; this organism was present in the nasopharynx and absent in the air in 6.5 per cent and was present in the air and absent in the nasopharynx in 6.5 per cent. Ruling out the positive cultures of sediment from the air or material from the nasopharynx which occurred alone but immediately preceding or following a week in which cultures both of sediment from the air and of material from the nose and throat yielded bacteria, there were only one isolated culture of sediment from the air (Feb. 16) and one isolated culture of material from the nose and throat (April 20) which yielded bacteria, or only 4 per cent of the total number of weekly cultures made.

On only two occasions, however, were they found singly except during the week immediately preceding or following a week when they were

cultured both from the air and from the nose and throat. As has been shown by Meleney and his colleagues [4] and by Walker [2d] from cultures of streptococci and by this and the previous report by one of us (D. H.)[1] for staphylococci, there is generally a low level of contamination by organisms in the air and in the nose and the throat during the summer.

It seems apparent from these cultures that there is a definite correlation as to both the type and the number of organisms found in the air of a given room and in the noses and throats of a group of regular occupants of that room. The question has been raised whether the noses and throats are contaminated by the organisms floating in the air in the room rather than that the air becomes contaminated by organisms from the nose and throat. Unquestionably infections may be, and probably most infections of the respiratory tract are, transmitted by this route. On the other hand, it seems most likely that the pathogenic bacteria found in the air have been given off from the noses and throats of carriers. As is shown in chart 2 and as has been repeatedly observed on other occasions, a Petri dish (with a surface measuring 63.4 sq. cm. [9.83 square inches]) of blood agar exposed to sedimentation for one hour in a room that has been closed and free of occupants for twelve hours or longer will show, on incubation, results varying from no growth up to four or five colonies of organisms, most commonly Staph. albus or Proteus vulgaris. The count is always low, even if the air and dust are agitated by electric fans, but it rises rapidly as soon as the room is occupied. From this it would seem that organisms die out rather than multiply in a room that has become contaminated and that bacteria must be brought in by the occupants. Material from shoes, hair, clothing, walls and the dust of the room has been cultured, but relatively few organisms have been found. Staph. albus in large numbers may be cultured from material from the skin, but the number and type of colonies cultured from material taken from the nose and throat seem to parallel more nearly the number and type of colonies cultured from sediment from the air. It also seems more logical that organisms should be expelled by the air currents from the respiratory passages than that they should come off the skin, which frequently is moist and usually is covered by a gown.

This work, undertaken to study the bacterial flora floating in the air of an occupied room and to compare this with the organisms found in the noses and throats of its occupants, has shown other interesting data. At certain times Str. viridans was found in tremendous numbers in cultures of material from the nose and throat. During such periods the bacteriologic laboratory reported that all cultures of pharyngeal material, from resident as well as from ambulatory patients, showed

4. Meleney.[2a,c] Meleney and Stevens.[2b]

a similar high level of contamination with this organism. Coincidentally, several of the experimental personnel had infections of the upper part of the respiratory tract, and the number of patients admitted to the hospital with such infections was large.

Comparison of data on the weather with the charted number of organisms showed a definite increase in contamination of the nose, the throat and the air after several days of rain. Conversely, after a period of bright, clear weather (regardless of temperature) the level of contamination in the nasopharynx and in the air was lower.

During the several years that we have more or less regularly cultured sediment from the air of the operating room and occasionally cultured material from the noses and throats of the personnel, as well as in the weekly cultures reported in this paper, Streptococcus haemolyticus beta has only rarely been found in the cultures of material from the throat. Reports in the literature lead us to believe that this organism may be more prevalent in certain other parts of the United States.[2d] During this time we have had virtual freedom from streptococcic wound infections. On the contrary, Staph. aureus haemolyticus has been the most virulent and the most frequent pathogenic organism found by us in the nasopharynx and in the air (charts 1 and 4) and has caused over 90 per cent of infections in supposedly clean operative wounds coming under our observation. With us this reached its peak in 1933-1934. The widespread distribution of this organism and the number and severity of the wound infections caused by it forced us to try various measures for its control. Bactericidal irradiation to sterilize the contaminated air has been the most effective of these, giving satisfactory results when all other measures have failed, at least partly.[5] In another hospital, located in the notheastern portion of the United States, where cultures showed Staph. aureus to be present in the air in large numbers,[6] there were 3 wound infections with this organism during the three week period during which cultures were made. The widespread distribution of this organism in the air of the operating rooms has been

5. (*a*) Hart, D.: Sterilization of the Air in the Operating Room with Bactericidal Radiation: A Comparative Analysis of One Hundred and Thirty-Two Individual Stages of Extrapleural Thoracoplasties Performed with Radiation and One Hundred and Ten Stages Performed Without Radiation, J. Thoracic Surg. **7**:525-535 (June) 1938; (*b*) Sterilization of the Air in the Operating Room by Bactericidal Radiant Energy: Results in Over Eight Hundred Operations, Arch. Surg. **37**:956 (Dec.) 1938. (*c*) Hart, D., and Sanger, P. W.: Effect on Wound Healing of Bactericidal Ultraviolet Radiation from a Special Unit: Experimental Study, ibid., to be published. (*d*) Hart, D.; Devine, J. W., and Martin, D. W.: Bactericidal and Fungicidal Effect of a Special Ultraviolet Radiation Unit Used for Sterilizing the Air in the Operating Room, ibid., to be published.

previously reported.[6] Should Str. haemolyticus beta become a common contaminant of the nasopharynx in this or any section we should expect an increase in the number of wound infections with this organism. A report by Walker [2d] from a teaching hospital in Boston demonstrates this clearly. With a rise in the number of carriers of Str. haemolyticus beta to between 25 and 50 per cent the incidence of streptococcic wound infections rose from a base line of zero during May, June, July and August to 10.5 per cent during March. At the same time the total number of infections rose from a base line of 8 per cent (average) during May through August to 42 per cent during March. In the same article, Walker reported that in sixteen hospitals in which seasonal epidemics of wound infections were said to have occurred the average rise was from a base level of 1.25 per cent during May through August to a peak of 8 per cent during March. It seems certain both from our experience and from the reports in the literature that in different places and at different times in the same place there are wide variations in the type of organism in the nose and throat and in the intensity of its growth. This is well illustrated by the widespread distribution of streptococci during the epidemic of influenza in 1918, at which time in certain places it was necessary to close the operating rooms for all except emergency operations. It seems that infections in clean operative wounds roughly follow this curve of incidence contamination of the respiratory tract. Many physicians are familiar with instances of operating room infections caused by the same organism which have reached almost epidemic proportions. In many instances these organisms must come from the nasopharyngeal passages of the personnel. We are convinced that in the majority of cases of so-called unexplained operating room infections, even when the conventional gauze mask is worn over both the mouth and the nose of every occupant, organisms from the respiratory tract are the cause of the infection and reach the wound and sterile supplies by way of the air rather than by contact.

SUMMARY

1. Staphylococci can be cultured readily from the air of an occupied room and furnish a fair index of the degree of contamination of the air.

2. The bacterial flora sedimenting from the air of a given room and that cultured from the mucous membranes of the noses and throats of the occupants of the room show a close similarity both as to number and as to type of organisms.

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6. Hart, D.: Pathogenic Bacteria in the Air of Operating Rooms: Their Widespread Distribution and the Methods of Control, Arch. Surg. **37**:521-530 (Oct.) 1938.

3. When nasopharyngeal contamination in the experimental group is at a high level the same condition is found to exist in patients, students and other groups of persons.

4. With occupancy of a room there is a rapid rise in the number of viable bacteria floating in the air, the number and type of bacteria being dependent on the number of occupants and the intensity of the growth in their noses and throats.

5. With termination of occupancy there is a moderately rapid diminution in the number of viable organisms sedimenting from the air, so that in from twelve to twenty-four hours the number is negligible.

6. There is a definite seasonal variation in contamination of the nose, the throat and the air by both pathogenic and nonpathogenic organisms, the level of such contamination being lower in clear, dry weather than when it is wet and cloudy. The lowest contamination over a relatively prolonged period occurs during the warmer months.

CONCLUSIONS

In the modern operating room the noses and throats of the occupants are the chief source of contamination of the air and the operative wound, despite the use of the conventional gauze mask worn over the nose and mouth. Organisms reach the wound and sterile supplies predominantly by way of the air, since transfer of organisms by direct contact has been largely eliminated by so-called aseptic surgical technic. Until contamination of the air with pathogenic bacteria can be prevented it seems imperative that the air in the operating room should be sterilized. Bactericidal irradiation offers a practical method of accomplishing this.